**Supporting Information**

# Efficient Synthesis of 4-Pyridone-3-carboxylic Acids *via* the Reaction of Enaminated Diketonates with Primary Amines

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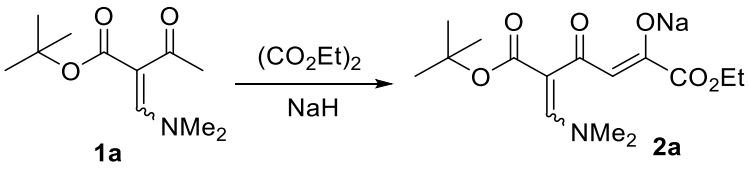
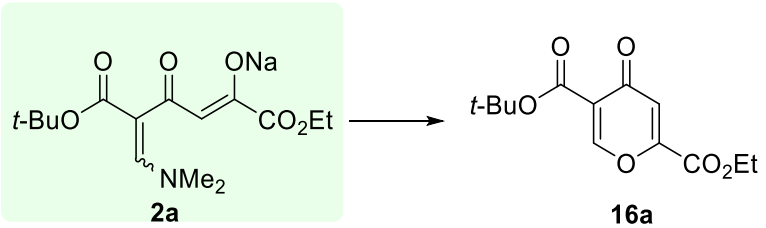
**Table 1S.** Optimization of the reaction conditions for the synthesis of diketonate **2a**




| № | Equiv. of $(CO_2Et)_2$ | Base | NaH | Solvent | Temperature, °C | Yield, % |
|---|---|---|---|---|---|---|
| **1** | **1.2** | **NaH** | **1.2** | **dioxane** | **70** | **99** |
| 2 | 1.2 | NaH | 1.8 | dioxane | 70→rt | 23 |
| 3 | 1.2 | NaH | 1.2 | THF | 70 | 83 |
| 4 | 1.2 | NaH | 1.2 | PhMe | rt→70 | 70 |
| 5 | 1.2 | *t*-BuOK | 1.2 | THF | rt | 74[a] |
| 6 | 1.2 | *t*-BuONa | 1.2 | THF | rt | 60 |
| 7 | 1.2 | NaH | 1.2 | $Et_2O$ | rt→70 | 93 |
| 8 | 1.2 | NaH | 1.2 | DME | rt→70 | 99 |

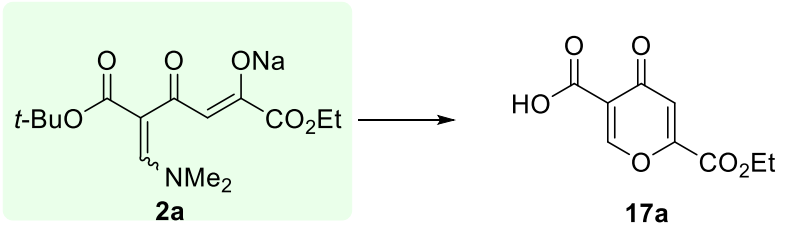
[a] The solid was unstable.

**Table 2S.** Optimization of the reaction conditions for the preparation of *tert*-butyl 4-pyrone-3-carboxylate **16a**.




| № | Conditions | Yield, % |
|---|---|---|
| 1 | EtOAc, $KHSO_4$ (5 equiv.), rt | 47 |
| 2 | EtOAc, $KHSO_4$ (5 equiv.), 0 °C → rt | 38 |
| 3 | $CH_2Cl_2$, $KHSO_4$ (5 equiv.), 0 °C → rt | 69 |
| **4** | **$CH_2Cl_2$, $KHSO_4$ (5 equiv.), 0 °C** | **80** |

**Table 3S.** Optimization of the reaction conditions for the synthesis of 4-pyrone-3-carboxylic acid **17a**




| № | Conditions | Yield, % |
|---|---|---|
| 1 | EtOAc, $CF_3CO_2H$ (5 equiv.), 0 °C → rt | 13 |
| 2 | $CH_2Cl_2$, $CF_3CO_2H$ (3 equiv.), 0 °C → rt | 53 |
| 3 | $CH_2Cl_2$, $CF_3CO_2H$ (4 equiv.), 0 °C → rt | 64 |
| **4** | **$CH_2Cl_2$, $CF_3CO_2H$ (10 equiv.), 0 °C → rt** | **72** |
| 5 | $CH_2Cl_2$, $MeSO_3H$ (3 equiv.), 0 °C → rt | 69 |

## General information

NMR spectra were recorded on Bruker DRX-400 ($^1$H, 400 MHz; $^{13}$C, 101 MHz), Bruker Avance-400 ($^1$H, 400 MHz; $^{13}$C, 101 MHz), Bruker Avance III-500 ($^1$H, 500 MHz; $^{13}$C, 126 MHz) and Bruker Avance NEO ($^1$H, 600 MHz; $^{13}$C, 151 MHz) spectrometers in DMSO-$d_6$ or $CDCl_3$. The chemical shifts (δ) are reported in ppm relative to the internal standard TMS ($^1$H NMR) and residual signals of the solvents ($^{13}$C NMR). IR spectra were recorded on a Shimazu IRSpirit-T spectrometer using an attenuated total reflectance (ATR) unit (FTIR mode, diamond prism), the absorbance maxima (ν) are reported in $cm^{-1}$. Optical rotations were measured on a Perkin Elmer M341 polarimeter.

Mass spectra (ESI-MS) were measured with a Waters Xevo QTof instrument and the UHR-QqTOF maXis Impact HD (Bruker Daltonics) mass spectrometer. Elemental analyses were performed on an automatic analyzer PerkinElmer PE 2400. Melting points were determined using a Stuart SMP40 melting point apparatus. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). All solvents that were used were dried and distilled by standard procedures.

***Tert*-butyl 2-((dimethylamino)methylene)-3-oxobutanoate (1)** [1].

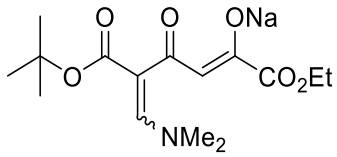
*Tert*-butyl-3-oxobutanoate and 1.2 equivalents of dimethylformamide dimethylacetal (DMF-DMA) were mixed at room temperature and heated at 80 °C for 2 h, the resulting product was distilled with the use of a vacuum pump at 110–120 °C.

**General method for the preparation of enaminated diketonates 2**

Sodium hydride (60% suspension in mineral oil) (0.79 g, 19.7 mmol) was added gradually in portions to solution of *tert*-butyl-2-((dimethylamino)methylene)-3-oxobutanoate (**1a**) (3.5 g, 16.4 mmol) and the corresponding carboxylic acid ester (19.7 mmol) in dry dioxane (6 mL) under stirring and ice-cooling. After the end of hydrogen evolution, the reaction was stirred at room temperature until a precipitate formed. The product was filtered and washed with toluene.

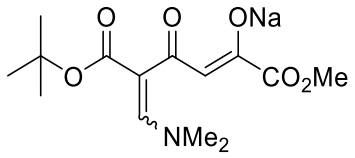
For compounds **2a** and **2b**, the condensation was carried under heating at 70 °C for the initiation of the reaction.

**Sodium 5-(*tert*-butoxycarbonyl)-6-(dimethylamino)-1-ethoxy-1,4-dioxohexa-2,5-dien-2-olate (2a).**



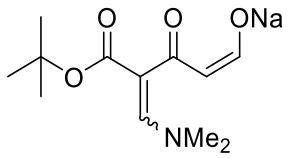

Yield 99% (5.44 g), beige solid, mp 210–211 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.07 (s, 1H, H-6), 5.69 (s, 1H, H-3), 4.05 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.87 (s, 6H, $NMe_2$), 1.54–1.42 (m, 9H, *t*-Bu), 1.20 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 190.8 (br.s), 168.8, 166.7 (br.s), 151.5, 105.7 (br.s), 102. (br.s), 96.8 (br.s), 78.9 (br.s), 61.1, 43.4, 28.3, 14.2, 2C were not observed due to broadening; IR (ATR): 2978, 2920, 1657, 1595, 1363, 1213, 1128, 785 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{15}H_{23}NO_6Na^+$ $(M+H)^+$ 336.1423; found: 336.1416.

**Sodium 5-(*tert*-butoxycarbonyl)-6-(dimethylamino)-1-methoxy-1,4-dioxohexa-2,5-dien-2-olate (2b).**



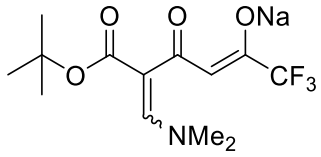

Yield 99% (5.22 g), beige solid, mp 205–206 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H, H-6), 5.96 (s, 1H, H-3), 3.71 (s, 3H, Me), 2.88 (br.s, 6H, $NMe_2$), 1.44 (br.s, 9H, *t*-Bu); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 190.6 (br.s), 169.2 (br.s), 161.8 (br.s), 151.2 (br.s), 105.3 (br.s), 102.2 (br.s), 97.0 (br.s), 78.8 (br.s), 52.1 43.4 (br.s), 28.3; IR (ATR): 2977, 2932, 1653, 1390, 1363, 1218, 786 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{14}H_{21}NO_6Na^+$ $(M+H)^+$ 322.1280; found: 322.1265.

**Sodium 4-(*tert*-butoxycarbonyl)-5-(dimethylamino)-3-oxopenta-1,4-dien-1-olate (2c).**



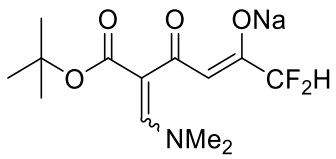
Yield 99% (4.27 g), yellow solid, mp 155–156 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.72 (br.d, 1H, $J$ = 10.1 Hz, H-5), 6.92 (s, 1H, H-2), 4.63 (d, $J$ = 10.1 Hz, 1H, H-1), 2.86 (s, 6H, $NMe_2$), 1.32 (s, 9H, *t*-Bu); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 184.9, 168.1, 166.5, 146.7, 107.5, 104.3, 76.4, 66.3, 41.4, 28.3; IR (ATR): 2928, 1634, 1386, 1351, 1064, 779 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{12}H_{19}NO_4Na^+$ $(M+H)^+$ 264.1212; found: 264.1223.

**Sodium 5-(*tert*-butoxycarbonyl)-6-(dimethylamino)-1,1,1-trifluoro-4-oxohexa-2,5-dien-2-olate (2d).**



Yield 99% (5.38 g), light yellow solid, mp 145–146 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H, H-6), 5.24 (s, 1H, H-3), 2.89 (s, 6H, $NMe_2$), 1.41 (s, 9H, *t*-Bu); $^{19}$F NMR (376 MHz, $CDCl_3$) δ 84.7; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 190.7, 168.2, 152.3, 119.7 (q, $J$ = 288.2 Hz), 104.3, 97.6, 92.7, 79.4, 43.7, 28.3; IR (ATR): 2978, 1723, 1683, 1427, 1128 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{13}H_{18}NO_4F_3Na^+$ $(M+H)^+$ 332.1086; found: 332.1085.

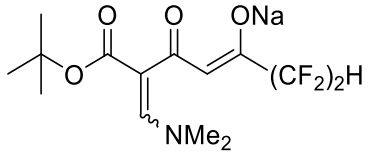
**Sodium 5-(*tert*-butoxycarbonyl)-6-(dimethylamino)-1,1-difluoro-4-oxohexa-2,5-dien-2-olate (2e).**



Yield 99% (5.09 g), light yellow solid, mp 138–139 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H, H-6), 5.63 (d, $J$ = 56.6 Hz, 1H, $CF_2H$), 5.21 (s, 1H, H-3), 2.89 (s, 6H, $NMe_2$), 1.42 (s, 9H, *t*-Bu); $^{19}$F NMR (376 MHz, $CDCl_3$) δ 37.2 (br.s); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 189.8 (br.s), 176.4 (br.s), 168.9, 151.0, 112.5 (t, $J$ = 248.8 Hz), 104.7, 98.5, 79.1, 43.6 (br.s), 28.3; IR (ATR): 2978,

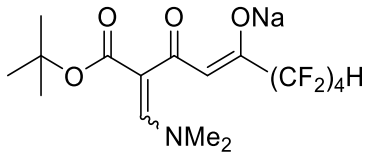
2928, 1665, 1633, 1389, 1255, 1054, 797 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{13}H_{19}NO_4F_2Na^+$ $(M+H)^+$ 314.1191; found: 314.1187.

**Sodium 6-(*tert*-butoxycarbonyl)-7-(dimethylamino)-1,1,2,2-tetrafluoro-5-oxohepta-3,6-dien-3-olate (2f).**



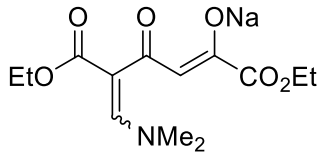

Yield 99% (5.89 g), light yellow solid, mp 143–144 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H, H-7), 6.14 (t, $J$ = 52.6 Hz, 1H, $CF_2H$), 5.31 (s, 1H, H-4), 2.90 (s, 6H, $NMe_2$), 1.41 (s, 9H, *t*-Bu); $^{19}F$ NMR (376 MHz, DMSO-$d_6$) δ 38.6 (d, $J$ = 87.4 Hz), 23.0 (dt, $J$ = 53.2, $J$ = 9.2 Hz); $^{13}C$ NMR (126 MHz, DMSO-$d_6$), two isomers: δ 187.9, 182.9, 169.1, 167.6 149.6, 148.0, 114.4–110.4 ($CF_2$), 110.4 (tt, $J$ = 247.4 Hz, $J$ = 33.7 Hz), 96.7, 89.4, 79.0, 77.0, 66.3, 42.4, 28.1, 27.5; IR (ATR): 2970, 2923, 1656, 1392, 1231, 1161, 1101, 791 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{14}H_{19}NO_4F_4Na^+$ $(M+H)^+$ 364.1148; found: 364.1143.

**Sodium 2-(*tert*-butoxycarbonyl)-1-(dimethylamino)-6,6,7,7,8,8,9,9-octafluoro-3-oxonona-1,4-dien-5-olate (2g).**




Yield 99% (7.52 g), yellow solid, mp 118–119 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, H-1), 6.24 (t, $J$ = 52.2 Hz, 1H, $CF_2H$), 5.26 (s, 1H, H-5), 2.90 (s, 6H, $NMe_2$), 1.41 (s, 9H, *t*-Bu); $^{19}F$ NMR (376 Hz, $CDCl_3$) δ 42.2, 35.7, 30.8, 23.9 (d, $J$ = 53.4 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 190.1, 170.0, 168.6, 152.7, 114.0–108.6 (m, $3CF_2$), 107.7 (tt, $J$ = 252.8 Hz, $J$ = 30.6 Hz), 103.1, 99.3, 79.7, 43.7, 28.2; IR (ATR): 2925, 1657, 1392, 1368, 1226, 1163, 796 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{16}H_{19}NO_4F_8Na^+$ $(M+H)^+$ 464.1099; found: 464.1102.

**Sodium 6-(dimethylamino)-1-ethoxy-5-(ethoxycarbonyl)-1,4-dioxohexa-2,5-dien-2-olate (2h).**



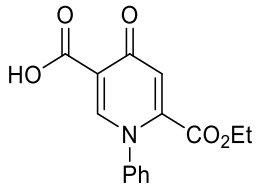
Sodium *tert*-butoxide (0.31 g, 3.2 mmol) was added gradually to solution of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate (0.50 g, 2.7 mmol) and diethyl oxalate (0.47 g, 3.2 mmol) in dry dioxane (0.2 mL). The reaction was stirred at room temperature until a precipitate formed. The resulting precipitate was filtered and was washed with THF. Yield 93% (0.83 g), beige solid, mp 220 °C (dec.). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24–7.04 (s, 1H, H-1), 5.65 (s, 1H, H-5), 4.18–3.80 (m, 4H, $2CH_2$) 2.92–2.84 (br.s, 6H, $NMe_2$), 1.30–1.02 (m, 6H, 2Me). The spectrum is in accordance with the literature [2].

**General method for the preparations of compounds 3,4**

The corresponding amine (0.36 mmol) was added to a solution of diketonate **2** (0.33 mmol) in AcOH (1 mL). The resulting solution was stirred at room temperature for 24 h, then was refluxed at 120 °C for 6 h. The solvent was evaporated at room temperature, the residue was treated with water, and the precipitate was filtered.

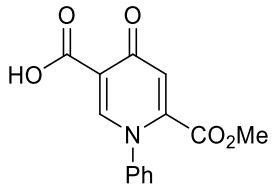
In the case of fluorine-containing compounds **3d–g**, **4d–f**, **7d**, the reaction mixture was stirred for 3 days at room temperature.

**6-(Ethoxycarbonyl)-4-oxo-1-phenyl-1,4-dihydropyridine-3-carboxylic acid (3a).**



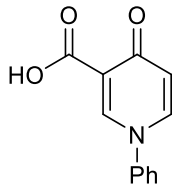
Yield 92% (0.079 g), beige solid, mp 174–175 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 14.89 (s, 1H, OH), 8.60 (s, 1H, H-2), 7.60–7.52 (m, 3H, Ph), 7.32 (dd, $J$ = 7.6, $J$ = 2.0 Hz, 2H, H-2, H-6 Ph), 7.21 (s, 1H, H-5), 4.14 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.07 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 179.1, 165.4, 160.5, 148.0, 143.2, 141.7, 130.3, 130.1, 125.0, 122.0, 117.2, 63.4, 13.5; IR (ATR): 3076, 2992, 1634, 1595, 1475, 1394, 1271, 1126, 941, 856, 783, 712 cm$^{-1}$; Anal. calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88; found: C, 62.71; H, 4.67; N, 4.91.

**6-(Methoxycarbonyl)-4-oxo-1-phenyl-1,4-dihydropyridine-3-carboxylic acid (3b).**



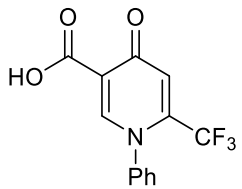
Yield 91% (0.080 g), beige solid, mp 172–173 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 14.84 (s, 1H, OH), 8.61 (s, 1H, H-2), 7.66–7.50 (m, 3H, Ph), 7.33–7.29 (m, 2H, Ph), 7.23 (s, 1H, H-5), 3.72 (s, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 179.1, 165.4, 161.0, 148.2, 142.6, 141.6, 130.4, 130.1, 125.0, 122.3, 117.3, 53.8; IR (ATR): 3065, 3050, 2960, 1721, 1630, 1594, 1469, 1288, 1262, 1229, 1175, 940, 762 $cm^{-1}$; Anal. calcd for $C_{14}H_{11}NO_5 \cdot 0.25H_2O$: C, 60.54; H, 4.17; N, 5.04; found: C, 60.30; H, 3.85; N, 5.13.

**4-Oxo-1-phenyl-1,4-dihydropyridine-3-carboxylic acid (3c).**



Yield 56% (0.040 g), beige solid, mp 262–263 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, $J$ = 2.4 Hz, 1H, H-2), 7.82 (dd, $J$ = 7.6 Hz, $J$ = 2.4 Hz, 1H, H-6), 7.67–7.55 (m, 3H, Ph), 7.45–7.41 (m, 2H, H-2, H-6 Ph), 6.86 (d, $J$ = 7.6 Hz, 1H, H-5), the OH proton was not observed due to broadening; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 179.1, 166.2, 144.9, 142.3, 141.1, 130.7, 130.1, 123.2, 120.2, 117.2; IR (ATR): 3058, 1700, 1635, 1487, 1180, 925 $cm^{-1}$; Anal. calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51; found: C, 67.75; H, 4.38; N, 5.97.

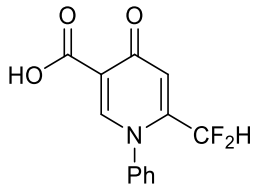
**4-Oxo-1-phenyl-6-(trifluoromethyl)-1,4-dihydropyridine-3-carboxylic acid (3d).**



Yield 95% (0.080 g), beige solid, mp 204–205 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 14.91 (s, 1H, OH), 8.50 (s, 1H, H-2), 7.70 (d, $J$ = 7.6 Hz, 2H, H-2, H-6 Ph), 7.66–7.55 (m, 3H, Ph), 7.45 (s, 1H, H-5); $^{19}$F NMR (471 Hz, DMSO-$d_6$) δ 102.1; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.4, 164.3, 150.2, 139.7, 139.6 (d, $J$ = 34.7 Hz, C-6), 130.9, 129.9, 127.5, 119.3 (q, $J$ = 4.5 Hz, C-5), 119.0 (q, $J$ = 275.5 Hz, $CF_3$), 116.1; IR (ATR): 3073, 1720, 1770, 1645, 1597, 1475, 1310, 1171, 1109,

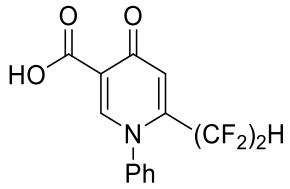
1055, 1002, 766 $cm^{-1}$; Anal. calcd for $C_{13}H_8F_3NO_3 \cdot 0.25H_2O$: C, 54.27; H, 2.98; N, 4.87; found: C, 54.61; H, 2.78; N, 4.91.

**6-(Difluoromethyl)-4-oxo-1-phenyl-1,4-dihydropyridine-3-carboxylic acid (3e).**



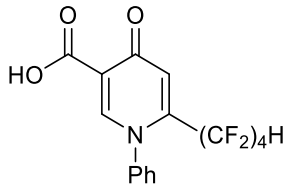

Yield 75% (0.064 g), beige solid, mp 190–191 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 14.82 (s, 1H, OH), 8.54 (s, 1H, H-2), 7.71–7.54 (m, 3H, Ph), 7.40 (dd, *J* = 7.3 Hz, *J* = 2.1 Hz, 2H, H-2, H-6 Ph), 7.15 (s, 1H, H-5), 6.23 (t, *J* = 52.7 Hz, 1H, $CF_2H$); $^{19}$F NMR (376 Hz, $CDCl_3$) δ 45.0 (d, *J* = 52.7 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 179.1, 165.3, 148.1, 144.7 (t, *J* = 26.4 Hz, C-6), 138.5, 131.5, 130.6, 126.8, 118.3 (t, *J* = 5.5 Hz, C-5), 117.1, 108.2 (t, *J* = 243.1 Hz, $CF_2H$); IR (ATR): 3077, 2925, 2854, 1716, 1644, 1595, 1540, 1458, 1190, 1100, 1054, 793, 763 $cm^{-1}$; Anal. calcd for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.42; N, 5.28; found: C, 58.82; H, 3.54; N, 5.33.

**4-Oxo-1-phenyl-6-(1,1,2,2-tetrafluoroethyl)-1,4-dihydropyridine-3-carboxylic acid (3f).**



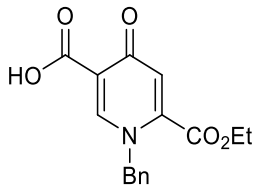

Yield 86% (0.089 g), beige solid, mp 182–183 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 14.54 (s, 1H, OH), 8.50 (s, 1H, H-2), 7.67–7.53 (m, 3H, Ph), 7.39 (d, *J* = 7.6 Hz, 2H, H-2, H-6 Ph), 7.18 (s, 1H, H-5), 5.57 (tt, *J* = 53.4 Hz, *J* = 3.6 Hz, 1H, $CF_2H$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ 53.4 (dt, *J* = 4.5 Hz, *J* = 3.6 Hz), 29.0 (dt, *J* = 53.0 Hz, *J* =4.5 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ177.9, 164.3, 150.6, 140.7, 140.5 (*J* = 25.0 Hz, C-6), 130.6, 129.3, 127.3, 120.8 (t, *J* = 6.0 Hz, C-5), 115.7, 111.8 (tt, *J* = 256.2 Hz, *J* = 25.7 Hz, $CF_2$), 108.8 (tt, *J* = 252.1 Hz, *J* = 32.9 Hz, $CF_2H$); IR (ATR): 3070, 2997, 1728, 1635, 1596, 1533, 1255, 1226, 1216, 1140, 1040, 840, 797 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{14}H_{10}F_4NO_3^+$ $(M+H)^+$ 316.0592, found: 316.0596.

**6-(1,1,2,2,3,3,4,4-Octafluorobutyl)-4-oxo-1-phenyl-1,4-dihydropyridine-3-carboxylic acid (3g).**



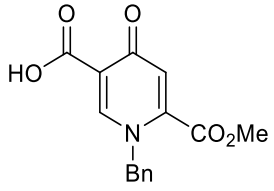
Yield 69% (0.062 g), beige solid, mp 109–110 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 14.81 (s, 1H, OH), 8.41 (s, 1H, H-2), 7.68 (d, $J$ = 7.6 Hz, 2H, H-2, H-6 Ph), 7.64–7.55 (m, 3H, Ph), 7.32 (s, 1H, H-5), 7.00 (tt, $J$ = 50.1 Hz, $J$ = 5.4 Hz, 1H, $CF_2H$); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 57.9 (t, $J$ = 13.2 Hz), 42.4 (t, $J$ = 8.2 Hz), 33.7 (m), 24.2 (d, $J$ = 50.3 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.6, 164.1, 151.0, 140.7, 139.0 (t, $J$ = 25.6 Hz, C-6), 130.6, 129.1, 127.4, 122.2 (t, $J$ = 6.5 Hz, C-5), 116.1, 112.6 (tt, $J$ = 261.0 Hz, $J$ = 36.3 Hz), 107.8 (t, $J$ = 251.5 Hz, $J$ = 30.6 Hz), 2$CF_2$ were not observed; IR (ATR): 3081, 1743, 1634, 1535, 1478, 1224, 1069, 1056, 1040, 896, 769 cm$^{-1}$; Anal. calcd for $C_{16}H_9F_8NO_3$: C, 46.28; H, 2.18; N, 3.37; found: C, 46.35; H, 2.27; N, 3.45.

**1-Benzyl-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (4a).**



Yield 76% (0.069 g), beige solid, mp 157–158 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 15.01 (s, 1H, OH), 8.67 (s, 1H, H-6), 7.42–7.34 (m, 3H, Ph), 7.20 (s, 1H, H-3), 7.16–7.09 (m, 2H, Ph), 5.58 (s, 2H, $CH_2$), 4.29 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 1.24 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 179.0, 165.7, 161.0, 148.6, 142.0, 133.9, 129.4, 129.2, 127.4, 123.5, 117.5, 63.6, 59.4, 13.8; IR (ATR): 3060, 1736, 1635, 1455, 1276, 1123, 1001, 904, 803, 750 cm$^{-1}$; Anal. calcd for $C_{16}H_{15}NO_5$: C, 63.47; H, 5.15; N, 4.64; found: C, 63.78; H, 5.02; N, 4.64.

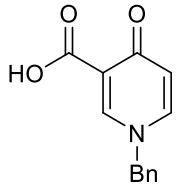
**1-Benzyl-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (4b).**



Yield 76% (0.068 g), beige solid, mp 156–157 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 15.3–14.3 (br.s, 1H, OH), 8.63 (s, 1H, H-2), 7.42–7.35 (m, 3H, Ph), 7.20 (s, 1H, H-3), 7.15–7.09 (m, 2H, Ph), 5.54 (s, 2H, $CH_2$), 3.83 (s, 3H, Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.9, 165.6, 161.5, 148.6, 141.5, 133.8, 129.4, 129.3, 127.4, 123.8, 117.6, 59.4, 53.9; IR (ATR): 3035, 2955, 1738, 1635, 1495,

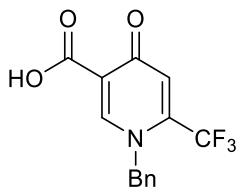
1262, 1148, 1128, 1084, 970 853, 800 $cm^{-1}$; Anal. calcd for $C_{15}H_{13}NO_5 \cdot 0.33H_2O$: C, 61.44; H, 4.70; N, 4.78; found: C, 61.72; H, 4.59; N, 4.77.

**1-Benzyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (4c).**



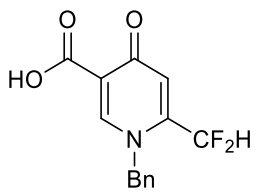
Yield 66% (0.050 g), yellow solid, mp 157–158 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 15.57 (s, 1H, OH), 8.59 (d, *J* = 2.4 Hz, 1H, H-2), 7.53 (dd, *J* = 7.5 Hz, *J* = 2.4 Hz, 1H, H-6), 7.48–7.40 (m, 3H, Bn), 7.25–7.22 (m, 2H, Bn), 6.74 (d, *J* = 7.5 Hz, 1H, H-5), 5.12 (s, 2H, $CH_2$-Ph); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.9, 166.5, 145.5, 141.4, 133.1, 129.70, 129.68, 127.9, 120.3, 116.9, 61.6; IR (ATR): 3060, 1640, 1559, 1467, 801, 722 $cm^{-1}$; Anal. calcd for $C_{13}H_{11}NO_3 \cdot 0.5H_2O$: C, 65.54; H, 5.08; N, 5.88; found: C, 65.74; H, 5.03; N, 5.60.

**1-Benzyl-4-oxo-6-(trifluoromethyl)-1,4-dihydropyridine-3-carboxylic acid (4d).**



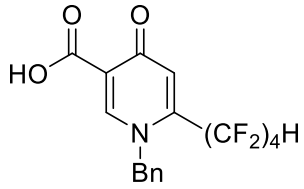
Yield 63% (0.056 g), beige solid, mp 112–113 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 14.6–14.2 (br.s, 1H, OH), 8.50 (s, 1H, H-2), 7.47–7.42 (m, 3H, Bn), 7.21 (s, 1H, H-5), 7.18–7.14 (m, 2H, Bn), 5.31 (s, 2H, $CH_2$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ 99.0; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 178.4, 164.8, 148.7, 140.1 (q, *J* = 34.8 Hz, C-6), 132.78, 129.8, 129.7, 127.2, 120.4 (q, *J* = 4.8 Hz, C-5), 119.4 (q, *J* = 274.6 Hz, $CF_3$), 118.5, 118.2, 58.2 (q, *J* = 2.5 Hz, $CF_3$); IR (ATR): 3055, 1723, 1663, 1334, 1277, 1196, 1030, 800 $cm^{-1}$. Anal. calcd for $C_{14}H_{10}F_3NO_3$: C, 56.47; H, 3.39; N, 4.71; found: C, 56.45; H, 3.29; N, 4.73.

**1-Benzyl-6-(difluoromethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (4e).**



Yield 75% (0.067 g), beige solid, mp 127–128 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 14.79 (s, 1H, OH), 8.56 (s, 1H, H-2), 7.49–7.40 (m, 3H, Bn), 7.18–7.13 (m, 2H, Bn), 7.01 (s, 1H, H-5), 6.48 (t, $J$ = 52.7 Hz, 1H, $CF_2H$), 5.33 (s, 2H, $CH_2$); $^{19}$F NMR (376 MHz, $CDCl_3$) δ 45.4 (d, $J$ = 52.8 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 178.8, 165.4, 148.6, 143.9 (t, $J$ = 23.8 Hz, C-6), 132.9, 129.9, 129.7, 126.9, 120.4 (t, $J$ = 6.9 Hz, C-5), 117.5, 109.9 (t, $J$ = 244.1 Hz, $CF_2H$), 58.0 (t, $J$ = 3.3 Hz, $\underline{C}H_2$); IR (ATR): 3061, 2988, 1717, 1642, 1496, 1223, 1075, 1036, 822 cm$^{-1}$; Anal. calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02; found: C, 59.79; H, 4.01; N, 5.00.

**1-Benzyl-6-(1,1,2,2,3,3,4,4-octafluorobutyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (4f).**

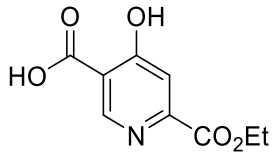



Yield 74% (0.068 g), beige solid, mp 119–120 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 14.88 (s, 1H), 8.87 (s, 1H, H-2), 7.44–7.39 (m, 2H, H-3, H-5 Ph), 7.38–7.33 (m, 1H, H-4 Ph), 7.32 (s, 1H, H-5), 7.17 (tt, $J$ = 50.2 Hz, $J$ = 5.3 Hz, 1H), 7.15 (d, $J$ = 7.8 Hz, 2H, H-2, H-6 Ph), 5.55 (s, 2H, $CH_2$); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.5, 164.3, 151.1, 138.8 (t, $J$ = 25.8 Hz, C-6), 135.7, 128.9, 128.1, 126.0, 123.1 (t, $J$ = 7.3 Hz, C-5), 117.3, 112.8 (tt, $J$ = 262.3 Hz, $J$ = 33.8 Hz, $CF_2$), 107.9 (tt, $J$ = 252.1 Hz, $J$ = 32.0 Hz), 58.8, 2$CF_2$ were not observed; IR (ATR): 3068, 2927, 1735, 1632, 1480, 1323, 1212, 1168, 1108,891,778 cm$^{-1}$; Anal. calcd for $C_{17}H_{11}F_8NO_3$: C, 47.57; H, 2.58; N, 3.26; found: C, 47.87; H, 2.61; N, 3.28.

**The method for the preparation of 4-hydroxynicotinic acids 5**

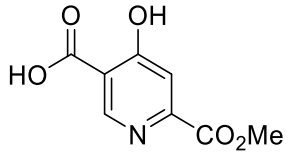
Diketonate **2** (0.33 mmol) and $NH_4OAc$ (0.051 g, 0.66 mmol) were added in AcOH (1 mL). The reaction mixture was stirred at room temperature for 24 h, then was refluxed at 120 °C for 6 h. After cooling, water (5 mL) was added, and the product was extracted with EtOAc (3x2 mL). The organic layer was washed with brine (2 mL) and was dried over anhydrous $MgSO_4$. The solvent was evaporated, and the product was recrystallized from toluene.

**6-(Ethoxycarbonyl)-4-hydroxynicotinic acid (5a).**



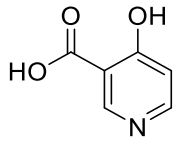
Yield 73% (0.050 g), beige solid, mp 257–258 °C. $^1$H NMR (500 MHz, $CDCl_3$), pyridinol tautomeric form: δ 8.73 (s, 1H, H-6), 7.41 (s, 1H, H-3), 4.51 (d, $J$ = 7.1 Hz, 2H, $CH_2$), 1.45 (t, $J$ = 7.1 Hz, 3H, Me), the OH protons were not observed due to broadening; $^1$H NMR (500 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 13.46 (s, 1H, NH), 8.44 (s, 1H, H-2), 7.22 (s, 1H, H-5), 4.41 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.36 (t, $J$ = 7.1 Hz, 3H, Me), the OH group was not observed due to broadening; $^{13}$C NMR (151 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 178.8, 166.0, 160.8, 144.2, 140.2, 119.8, 116.9, 63.5, 14.3; IR (ATR): 3082, 2982, 1728, 1685, 1585, 1477, 1392, 1215, 846, 794 cm$^{-1}$; Anal. calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63; found: C, 50.72; H, 4.21; N, 6.43.

**4-Hydroxy-6-(methoxycarbonyl)nicotinic acid (5b).**



Yield 71% (0.047 g), beige solid, mp 241–242 °C. $^1$H NMR (400 MHz, $CDCl_3$), pyridinol tautomeric form: δ 11.49 (s, 1H, OH), 8.59 (s, 1H, H-2), 7.69 (s, 1H, H-5), 4.01 (s, 3H, Me), the OH group was not observed due to broadening; $^{13}$C NMR (151 MHz, $CDCl_3$), pyridinol tautomeric form: δ 162.5, 137.9, 129.1, 128.2, 125.3, 35.0, 1C was not observed; IR (ATR): 3546, 3358, 3061, 2958, 2769, 1723, 1637, 1596, 1520, 1298, 1241, 1126, 982, 925, 786 cm$^{-1}$; Anal. calcd for $C_8H_7NO_5 \cdot H_2O$: C, 44.66; H, 4.22; N, 6.51; found: C, 44.39; H, 4.02; N, 6.52.

**4-Hydroxynicotinic acid (5c).**

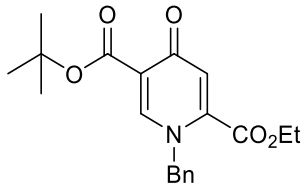


Yield 60% (0.032 g), beige solid, mp 259–260 °C. $^1$H NMR (500 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 16.83 (s, 1H, OH), 8.59 (d, $J$ = 1.4 Hz, 1H, H-2), 8.07 (dd, $J$ = 7.0 Hz, $J$ = 1.4 Hz, 1H, H-5), 6.68 (d, $J$ = 6.9 Hz, 1H, H-6), the NH proton was not observed due to broadening. The spectrum is in accordance with the literature data [3].

**General method for the preparation of esters 6,7**

Diketonate **2** (0.47 mmol) and amine (0.52 mmol) or acetate ammonium $NH_4OAc$ (0.046 g, 0.60 mmol) were dissolved in AcOH (1 mL). The reaction mixture was stirred for 24 h (for **7d** – 3 days) at room temperature. The solvent was evaporated in an evaporation dish. The residue was diluted with $H_2O$ (5 mL). The solid was filtered off and was recrystallized from hexane containing a little toluene.

**5-(*tert*-Butyl) 2-ethyl 1-benzyl-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (6a).**



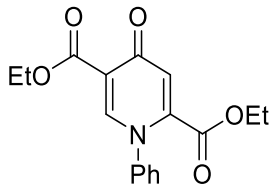

Yield 77% (0.082 g), beige solid, mp 119–120 °C.

*Mechanoactivation conditions*

Sodium 1-ethoxy-1,4-dioxohexa-2,5-dien-2-olate (**2a**) (0.100 g, 0.47 mmol), benzylamine (55.40 mg, 0.52 mmol) and AcOH (0.085 g, 1.41 mmol) were grinded in a mortar with the use of a pestle for 10 minutes (TLC monitoring). Then, the reaction was treated with water, and the resulting precipitate was filtered off. Yield 81% (0.087 g), beige solid, mp 119–120 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.48 (s, 1H, H-6), 7.38 (t, $J$ = 7.5 Hz, 2H, H-3, H-5 Ph), 7.32 (tt, $J$ = 7.3 Hz, $J$ = 1.3 Hz, 1H, H-4 Ph), 7.12 (d, $J$ = 8.0 Hz, 2H, H-2, H-6 Ph), 6.65 (s, 1H, H-3), 5.46 (s, 2H, $CH_2$-Ph), 4.14 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.48 (s, 9H, *t*-Bu), 1.09 (t, $J$ = 7.1 Hz, Me); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 175.4, 163.1, 162.0, 148.6, 139.1, 135.0, 129.2, 128.7, 127.1, 126.6, 120.8, 81.8, 62.8, 58.2, 28.2, 13.8; IR (ATR): 3065, 2985, 1670, 1631, 1555, 1456, 1361, 1217, 1093, 945, 794 cm$^{-1}$; Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; found: C, 67.50; H, 6.66; N, 4.30.

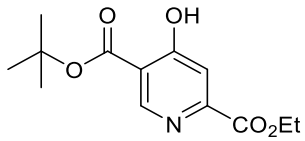
**Diethyl 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylate (6b).**




Yield 74% (0.077 g), yellow solid, mp 138–139 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.27 (s, 1H, H-6), 7.58–7.47 (m, 5H, Ph), 6.76 (s, 1H, H-3), 4.20 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 4.03 (q, J =

7.1 Hz, 2H, $CH_2$), 1.24 (t, $J$ = 7.1 Hz, 3H, Me), 0.94 (t, $J$ = 7.1 Hz, 3H, Me). The $^1$H NMR spectrum is in accordance with the literature data [2].

**5-(*tert*-Butyl) 2-ethyl 4-hydroxypyridine-2,5-dicarboxylate (7a).**



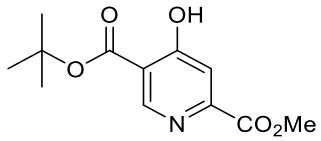

Yield 68% (0.055 g), beige solid, mp 166–167 °C.

*Mechanoactivation conditions*:

Diketonate **2a** (0.050 g, 0.150 mmol), $NH_4Cl$ (0.090 g, 0.165 mmol), and AcOH (0.027 g, 0.45 mmol) were grinded in a mortar for 10 minutes. Then, $H_2O$ were added, and the precipitate was filtered. Yield 58% (0.046 g), beige solid, mp 166–167 °C.

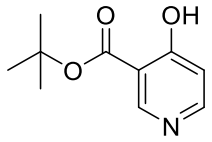
$^1$H NMR (500 MHz, $CDCl_3$), pyridinol tautomeric form: δ 11.47 (s, 1H, OH), 8.97 (s, 1H, H-6), 7.68 (s, 1H, H-3), 4.47 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 1.64 (s, 9H, *t*-Bu), 1.44 (t, $J$ = 7.2 Hz, 3H, Me); $^1$H NMR (500 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 12.6–11.4 (br.s, 1H, OH), 8.38 (s, 1H, H-6), 7.13 (s, 1H, H-3), 4.35 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.51 (s, 9H, *t*-Bu), 1.32 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, $CDCl_3$), pyridinol tautomeric form: δ 168.4, 168.2, 164.4, 152.4, 152.1, 114.5, 113.3, 84.9, 62.2, 28.1, 14.2; IR (ATR): 2982, 2929, 1716, 1685, 1635, 1392, 1168, 1059, 900, 846 cm$^{-1}$; Anal. calcd for $C_{13}H_{17}NO_5 \cdot 0.33H_2O$: C, 57.15; H, 6.52; N, 5.13; found: C, 57.14; H, 6.53; N, 5.10.

**5-(*tert*-Butyl) 2-methyl 4-hydroxypyridine-2,5-dicarboxylate (7b).**



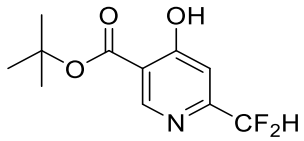

Yield 52% (0.041 g), beige solid, mp 186–187 °C. $^1$H NMR (500 MHz, $CDCl_3$), pyridinol tautomeric form: δ 11.49 (s, 1H, OH), 8.95 (s, 1H, H-6), 7.69 (s, 1H, H-3), 4.01 (s, 3H, Me), 1.69 (s, 9H, *t*-Bu); $^1$H NMR (500 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 8.39 (s, 1H, H-6), 7.14 (s, 1H, H-3), 3.89 (s, 3H, Me), 1.52 (s, 9H, *t*-Bu), the NH proton was not observed; $^{13}$C NMR (151 MHz, $CDCl_3$), pyridinol tautomeric form: δ 168.4, 168.3, 164.9, 152.1, 114.7, 113.4, 85.0, 53.2, 28.1; IR (ATR): 3073, 2977, 2928, 2854, 1725, 1653, 1585, 1446, 1364, 1065, 929, 841, 750 cm$^{-1}$; Anal. calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53; found: C, 56.38; H, 6.05; N, 5.38.

***tert*-Butyl 4-hydroxynicotinate (7c).**



Yield 52% (0.039 g), yellow solid, mp 213–214 °C. $^1$H NMR (400 MHz, $CDCl_3$), pyridinol tautomeric form: δ 11.38 (s, 1H, OH), 8.89 (s, 1H, H-2), 8.09 (s, 1H, H-5), 6.87 (d, $J$ = 5.9, 1H, H-6), 1.63 (s, 9H, *t*-Bu); $^1$H NMR (500 MHz, DMSO-$d_6$), pyridone tautomeric form: δ 8.16 (s, 1H, H-6), 7.69 (s, 1H, H-5), 6.24 (s, 1H, H-6), 1.48 (s, 9H, *t*-Bu); $^{13}$C NMR (126 MHz, $CDCl_3$), pyridinol tautomeric form: δ 169.0, 167.4, 154.4, 152.1, 112.8, 111.6, 84.1, 28.2; IR (ATR): 2976, 1730, 1693, 1628, 1585, 1550, 1366, 1143, 846 cm$^{-1}$; Anal. calcd for $C_{10}H_{13}NO_3 \cdot 0.25H_2O$: C, 60.14; H, 6.81; N, 7.01; found: C, 50.54; H, 6.54; N, 6.51.

***tert*-Butyl 6-(difluoromethyl)-4-hydroxynicotinate (7d).**



Yield 56% (0.044 g), yellow solid, mp 118–119 °C. $^1$H NMR (400 MHz, $CDCl_3$), pyridinol tautomeric form: δ 8.90 (s, 1H, H-2), 7.19 (s, 1H, H-5), 6.87 (d, $J$ = 5.9 Hz, 1H, H-6), 1.63 (s, 9H, *t*-Bu); $^{19}$F NMR (471 Hz, $CDCl_3$) δ 44.0 (d, $J$ = 55.2 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$), pyridinol tautomeric form: δ 168.5, 168.4, 157.5 (t, $J$ = 25.2 Hz, C-5), 152.2, 113.0 (t, $J$ = 241.5 Hz, $CF_2H$), 112.5, 109.5 (t, $J$ = 3.6 Hz, C-4), 84.9, 77.0 (t, $J$ = 32.0 Hz, C-6); IR (ATR): 3028, 2778, 1710, 1649, 1557, 1528, 1413, 1295, 1212, 1155, 1050, 880, 846 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{11}H_{13}F_2NO_3Na^+$ $(M+Na)^+$ 268.0756, found: 268.0761.

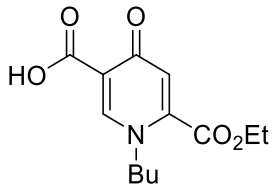
**General method for the preparation of 4-pyridone-3-carboxylic acids 8–12**

Diketonate **2a** (0.100 g, 0.30 mmol) and amine (0.30 mmol; for **10k** – 0.15 mmol) were stirred in AcOH (1 mL) for 24 h at room temperature. The reaction mixture was refluxed at 120 °C for 6 h. The solvent was evaporated at room temperature, and water was added. The solid was filtered off and was recrystallized from a mixture of toluene–hexane.

Compounds **8d**, **8g**, **9a**, and **11a** were isolated by extraction with EtOAc (3x2 mL). The combined organic layers were washed with water (3 mL), brine (3 mL) and dried with $MgSO_4$. The solvent was evaporated, and residue was recrystallized from a mixture of toluene–hexane.

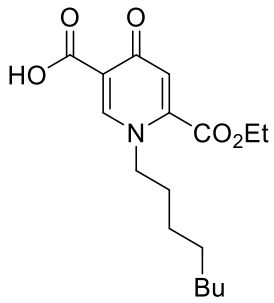
For compounds **12**, the precipitate was filtered and was washed with AcOH.

**1-Butyl-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8a).**



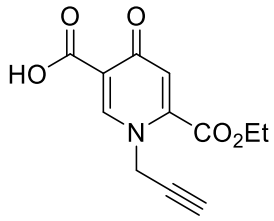
Yield 62% (0.050 g), white solid, mp 127–128 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.64 (s, 1H, OH), 8.85 (s, 1H, H-2), 7.18 (s, 1H, H-5), 4.40 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 4.37–4.33 (t, $J$ = 7.4 Hz, 2H, N-$CH_2$), 1.80–1.63 (m, 2H, $CH_2$), 1.34 (t, $J$ = 7.1 Hz, 3H, $CH_2$-Me), 1.27 (sextet, $J$ = 7.5 Hz, 2H, $CH_2$), 0.88 (t, $J$ = 7.4 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.1, 165.1, 160.8, 148.8, 142.9, 121.3, 116.4, 63.3, 55.4, 32.6, 18.9, 13.6, 13.4; IR (ATR): 3050, 2959, 2872, 1730, 1636, 1469, 1369, 1246, 1042, 923, 802, 778 cm$^{-1}$; Anal. calcd for $C_{13}H_{17}NO_5 \cdot 0.25H_2O$: C, 57.45; H, 6.49; N, 5.15; found: C, 57.78; H, 6.54; N, 5.06.

**6-(Ethoxycarbonyl)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8b).**



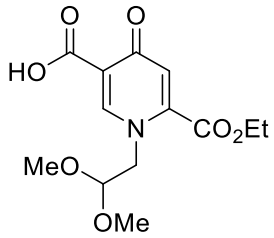
Yield 64% (0.065 g), beige solid, mp 126–127 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.64 (s, 1H, OH), 8.85 (s, 1H, H-2), 7.17 (s, 1H, H-5), 4.40 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 4.34 (t, $J$ = 7.7 Hz, 2H, N$CH_2$), 1.70 (quintet, $J$ = 7.5 Hz, 2H, C$H_2$), 1.34 (t, $J$ = 7.1 Hz, 3H, Me), 1.30–1.18 (m, 10H, 4C$H_2$), 0.85 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.1, 165.1, 160.8, 148.8, 142.9, 121.2, 116.3, 63.3, 55.6, 31.1, 30.5, 28.4, 28.3, 25.4, 22.0, 13.9, 13.6; IR (ATR): 3050, 2872, 2855, 1730, 1635, 1499, 1464, 1370, 1338, 1251, 1128, 802, 738 cm$^{-1}$; Anal. calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33; found: C, 63.33; H, 7.91; N, 4.47.

**6-(Ethoxycarbonyl)-4-oxo-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3-carboxylic acid (8c).**



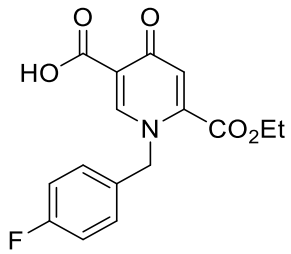
Yield 86% (0.064 g), beige solid, mp 162–163 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.32 (s, 1H, OH), 8.95 (s, 1H, H-2), 7.20 (s, 1H, H-5), 5.32 (d, $J$ = 2.5 Hz, 2H, $CH_2$), 4.40 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.77 (t, $J$ = 2.5 Hz, 1H, ≡CH), 1.35 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.5, 164.8, 160.5, 148.7, 142.1, 121.9, 116.3, 79.2, 77.1, 63.4, 45.3, 13.6; IR (ATR): 3284, 3056, 2129, 1706, 1642, 1493, 1442, 1394, 1371, 1011, 860, 802 cm$^{-1}$; Anal. calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62; found: C, 57.67; H, 4.57; N, 5.76. HRMS(ESI): m/z calcd for $C_{12}H_{11}NO_5K^+$ $(M+K)^+$ 288.0269, found: 288.0275.

**1-(2,2-Dimethoxyethyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8d).**




Yield 92% (0.082 g), beige solid, mp 103–104 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.49 (s, 1H, OH), 8.75 (s, 1H, H-2), 7.12 (s, 1H, H-5), 4.65 (d, $J$ = 4.1 Hz, 2H, $CH_2$N), 4.59 (t, $J$ = 4.1 Hz, 1H, CH), 4.35 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.30 (s, 6H, 2MeO), 1.34 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.4, 165.1, 161.1, 150.4, 143.8, 120.9, 115.7, 102.2, 62.9, 55.5, 55.1, 13.6; IR (ATR): 3060, 2947, 2844, 1731, 1627, 1490, 1392, 1254, 1150, 1075, 887 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{13}H_{17}NO_7Na^+$ $(M+Na)^+$ 322.0897, found: 322.0908.

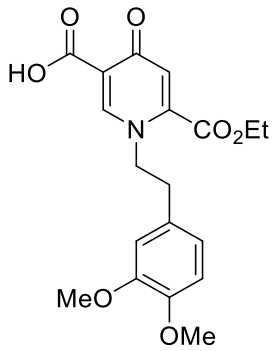
**6-(Ethoxycarbonyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8e).**




Yield 72% (0.069 g), beige solid, mp 185–186 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.46 (s, 1H, OH), 9.00 (s, 1H, H-2), 7.28–7.18 (m, 4H, Bn), 7.15 (s, 1H, H-5), 5.64 (s, 2H, $CH_2$-Ph), 4.19 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.12 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 48.90; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.4, 165.0, 161.8 (d, $J$ = 243.2 Hz, C-4 Ar), 160.8, 149.3, 142.9, 131.6 (d, $J$ = 3.0 Hz, C-4 Ar), 129.8 (d, $J$ = 8.5 Hz, C-2, C-6 Ar), 121.6, 116.4, 115.7 (d, $J$ = 21.6 Hz, C-3, C-5 Ar), 63.1, 57.4, 13.4; IR (ATR): 3055, 1738, 1636, 1602, 1510, 1494, 1150, 1125,

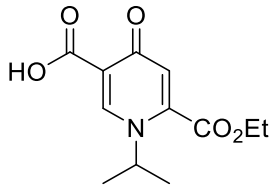
1042, 847 $cm^{-1}$; Anal. calcd for $C_{16}H_{14}FNO_5$: C, 60.19; H, 4.42; N, 4.39; found: C, 60.17; H, 4.52; N, 4.20.

**1-(3,4-Dimethoxyphenethyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8f).**



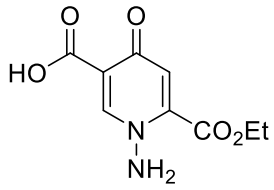

Yield 83% (0.093g), beige solid, mp 147–148 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 15.58 (s, 1H, OH), 8.78 (s, 1H, H-2), 7.13 (s, 1H, H-5), 6.85 (d, $J$ = 8.1 Hz, 1H, Ar), 6.80 (d, $J$ = 2.0 Hz, 1H, H-2 Ar), 6.62 (dd, $J$ = 8.1 Hz, $J$ = 2.0 Hz, 1H, Ar), 4.62 (t, $J$ = 7.2 Hz, 2H, $CH_2$), 4.30 (q, $J$ = 7.1 Hz, 2H), 3.70 (s, 3H, MeO), 3.71 (s, 3H, MeO), 2.96 (t, $J$ = 7.2 Hz, 2H, $CH_2$), 1.31 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.1, 165.0, 160.7, 149.0, 148.8, 147.8, 142.8, 128.7, 121.2, 121.1, 116.3, 112.8, 112.0, 63.3, 56.4, 55.5, 55.4, 36.2, 13.5; IR (ATR): 3050, 2937, 2837, 1733, 1637, 1515, 1332, 1125, 1028, 802 $cm^{-1}$; Anal. calcd for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64; N, 3.73; found: C, 60.66; H, 5.76; N, 3.53.

**6-(Ethoxycarbonyl)-1-isopropyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8g).**



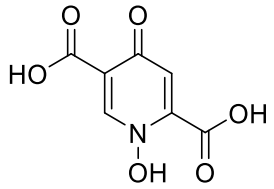

Yield 84% (0.064 g), beige solid, mp 78–79 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.70 (s, 1H, OH), 8.75 (s, 1H, H-2), 7.09 (s, 1H, H-5), 4.77 (septet, $J$ = 6.6 Hz, 1H, CH), 4.41 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.50 (d, $J$ = 6.6 Hz, 6H, 2Me), 1.35 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.9, 165.0, 161.1, 144.3, 143.4, 119.9, 116.9, 63.4, 57.1, 22.2, 13.6; IR (ATR): 3039, 2983, 2940, 1720, 1625, 1462, 1264, 1236, 1119, 1029, 915, 885, 801 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{12}H_{16}NO_5^+$ $(M+H)^+$ 254.1023, found: 254.1023.

**1-Amino-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (9a).**



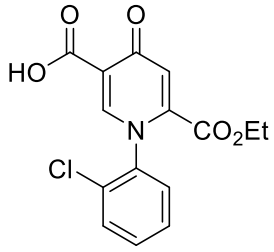
Yield 57% (0.039 g), beige solid, mp 196–197 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.85 (s, 1H, OH), 8.57 (s, 1H, H-2), 7.02 (s, 1H, H-5), 6.91 (s, 2H, $NH_2$), 4.37 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.33 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.5, 165.0, 160.2, 148.2, 146.2, 117.5, 115.3, 62.9, 13.7; IR (ATR): 3343, 3269, 3061, 1727, 1634, 1474, 1368, 1269, 1133, 1055, 1014, 924, 828 cm$^{-1}$; Anal. calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39; found: C, 47.87; H, 4.29; N, 12.37. HRMS(ESI): m/z calcd for $C_9H_{10}N_2O_5Na^+$ $(M+Na)^+$ 249.0482, found: 249.0489.

**1-Hydroxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylic acid (9b).**



Yield 72% (0.043 g), beige solid, mp 298–299 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 17.64 (s, 1H, OH), 8.42 (s, 1H, H-6), 7.24 (s, 1H, H-3), 2OH were not observed; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 172.6, 165.9, 161.6, 138.1, 138.0, 118.1, 116.8; IR (ATR): 3522, 3085, 1668, 1612, 1515, 1466, 1381, 1314, 1263, 1198, 1137, 1057, 935, 884 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_7H_6NO_6^+$ $(M+H)^+$ 200.0190, found: 200.0191.

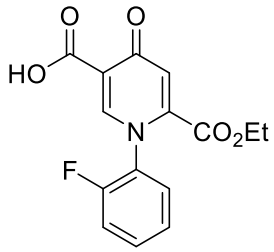
**1-(2-Chlorophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10a).**



Yield 73% (0.070 g), beige solid, mp 157–158 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.07 (s, 1H), 8.65 (s, 1H, H-2), 7.77 (dd, $J$ = 7.7 Hz, $J$ = 1.8 Hz, 1H, Ar), 7.72 (dd, $J$ = 7.9, $J$ = 1.6 Hz, 1H, Ar), 7.61 (td, $J$ = 7.8 Hz, $J$ = 1.8 Hz, 1H, Ar), 7.55 (td, $J$ = 7.6 Hz, $J$ = 1.6 Hz, 1H, Ar), 7.34 (s, 1H, H-5), 4.10 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.02 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.8, 164.4, 159.7, 149.1, 142.9, 138.6, 131.8, 130.0, 129.8, 128.7, 128.5, 121.1, 116.5,

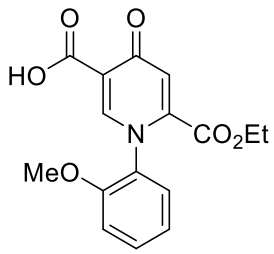
63.0, 13.2; IR (ATR): 3060, 3030, 2986, 1723, 1627, 1528, 1395, 1371, 1249, 1131, 1010, 926, 896, 864 $cm^{-1}$; Anal. calcd for $C_{15}H_{12}ClNO_5 \cdot 0.25H_2O$: C, 56.00; H, 3.76; N, 4.35; found: C, 55.83; H, 3.85; N, 4.24.

**6-(Ethoxycarbonyl)-1-(2-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10b).**




Yield 67% (0.061 g), beige solid, mp 131–132 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 15.04 (s, 1H, OH), 8.71 (s, 1H, H-2), 7.74 (td, $J$ = 7.9 Hz, $J$ = 1.6 Hz, 1H, Ar), 7.66–7.59 (m, 1H, Ar), 7.49 (ddd, $J$ = 10.3 Hz, $J$ = 8.4 Hz, $J$ = 1.3 Hz, 1H, Ar), 7.40 (t, $J$ = 7.6 Hz, 1H, Ar), 7.32 (s, 1H, H-5), 4.13 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.03 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 38.29 (ddd, $J$ = 10.3 Hz, $J$ = 7.9 Hz, $J$ = 5.3 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.8, 164.4, 159.9, 155.9 (d, $J$ = 249.1 Hz, C-2 Ar), 149.4, 142.9, 132.2 (d, $J$ = 8.0 Hz), 128.9 (d, $J$ = 12.7 Hz), 128.0, 125.4 (d, $J$ = 3.8 Hz), 121.0, 116.6, 116.4 (t, $J$ = 19.1 Hz), 63.0, 13.2; IR (ATR): 3218, 2988, 2875, 1723, 1630, 1530, 1454, 1372, 1291, 1215, 1111, 1064, 897, 767 $cm^{-1}$; Anal. calcd for $C_{15}H_{12}FNO_5 \cdot 0.25H_2O$: C, 56.00; H, 3.76; N, 4.35; found: C, 55.83; H, 3.85; N, 4.24.

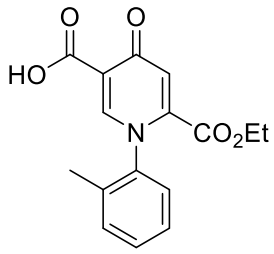
**6-(Ethoxycarbonyl)-1-(2-methoxyphenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10c).**




Yield 64% (0.061 g), beige solid, mp 192–193 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.24 (s, 1H, OH), 8.49 (s, 1H, H-2), 7.59 (dd, $J$ = 7.8 Hz, $J$ = 1.6 Hz, 1H, Ar), 7.54 (ddd, $J$ = 8.3 Hz, $J$ = 7.5 Hz, $J$ = 1.7 Hz, 1H, Ar), 7.24 (d, $J$ = 8.2 Hz, $J$ = 1.2 Hz, 1H, Ar), 7.23 (s, 1H, H-5), 7.13 (td, $J$ = 7.7 Hz, $J$ = 1.2 Hz, 1H, Ph), 4.10 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.78 (s, 3H, OMe), 1.01 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 164.7, 160.1, 152.7, 149.2, 144.0, 131.4, 130.1, 126.7, 121.0, 120.1, 116.3, 112.4, 62.7, 56.0, 13.3; IR (ATR): 3058, 2988, 2854, 1739, 1627, 1504,

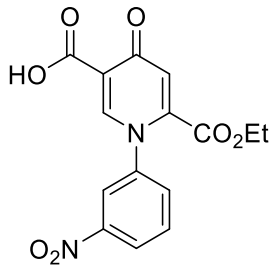
1452, 1372, 1289, 1193, 1020, 892, 802, 768 $cm^{-1}$; Anal. calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41; found: C, 60.65; H, 4.80; N, 4.38.

**6-(Ethoxycarbonyl)-4-oxo-1-(o-tolyl)-1,4-dihydropyridine-3-carboxylic acid (10d).**



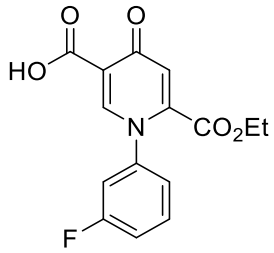
Yield 58% (0.052 g), beige solid, mp 126–127 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.32 (s, 1H, OH), 8.52 (s, 1H, H-2), 7.52–7.42 (m, 3H, Ar), 7.40–7.34 (m, 1H, Ar), 7.28 (s, 1H, H-5), 4.04 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.13 (s, 3H, Me-Ar), 0.93 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.6, 164.7, 160.1, 148.2, 143.9, 140.3, 134.2, 131.1, 130.3, 127.1, 126.7, 120.2, 116.4, 62.9, 16.8, 13.1; IR (ATR): 3045, 2986, 1724, 1629, 1524, 1456, 1368, 1200, 1009, 801, 772 $cm^{-1}$; Anal. calcd for $C_{16}H_{15}NO_6$: C, 63.78; H, 5.02; N, 4.65; found: C, 63.45; H, 5.15; N, 4.76.

**6-(Ethoxycarbonyl)-1-(3-nitrophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10e).**



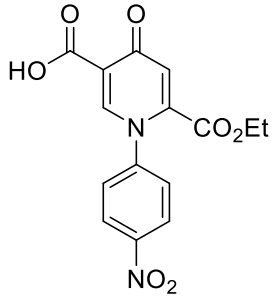
Yield 77% (0.077 g), yellow solid, mp 210–211 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) 15.22 (s, 1H, OH), 8.73 (s, 1H, H-2), 8.64 (t, $J$ = 2.2 Hz, 1H, H-2 Ar), 8.42 (ddd, $J$ = 8.3 Hz, $J$ = 2.2 Hz, $J$ = 0.9 Hz, 1H, H-4 Ar), 8.07 (ddd, $J$ = 8.0 Hz, $J$ = 2.1 Hz, $J$ = 0.9 Hz, 1H, H-6 Ar), 7.84 (t, $J$ = 8.2 Hz, 1H, H-5 Ar), 7.34 (s, 1H, H-2), 4.11 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.03 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.9, 164.6, 160.0, 149.3, 147.9, 142.5, 142.3, 132.7, 130.8, 124.5, 121.8, 121.2, 116.1, 63.1, 13.3; IR (ATR): 3059, 1714, 1653, 1548, 1444, 1350, 1278, 1111, 886, 801, 750 $cm^{-1}$; Anal. calcd for $C_{15}H_{12}N_2O_7 \cdot 0.33H_2O$: C, 53.27; H, 3.77; N, 8.28; found: C, 53.28; H, 3.61; N, 8.29.

**6-(Ethoxycarbonyl)-1-(3-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10f).**



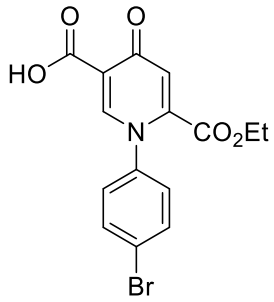
Yield 70% (0.065 g), beige solid, mp 177–178 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.22 (s, 1H, OH), 8.61 (dt, $J$ = 9.5 Hz, $J$ = 2.2 Hz, 1H, Ar), 7.64–7.57 (m, 1H, Ar), 7.48–7.42 (m, 2H, Ar), 7.27 (s, 1H, H-2), 4.11 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.03 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 52.04–50.98 (m); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 164.6, 161.8 (d, $J$ = 246.4 Hz, C-F), 160.2, 148.6, 143.2, 142.6 (d, $J$ = 10.7 Hz), 131.3 (d, $J$ = 9.0 Hz), 122.1 (d, $J$ = 3.3 Hz), 120.7, 116.9 (d, $J$ = 21.0 Hz), 116.0, 113.7 (d, $J$ = 25.3 Hz, C-3 Ar), 62.9, 13.2; IR (ATR): 3059, 2983, 2940, 1714, 1635, 1531, 1471, 1282, 1178, 1066, 969, 801 cm$^{-1}$; Anal. calcd for $C_{15}H_{12}FNO_5$: C, 59.02; H, 3.96; N, 4.59; found: C, 58.76; H, 4.01; N, 4.71.

**6-(Ethoxycarbonyl)-1-(4-nitrophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10g).**



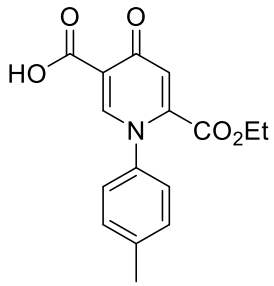
Yield 87% (0.087 g), yellow solid, mp 241–242 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.12 (s, 1H, OH), 8.68 (s, 1H, H-2), 8.41 (d, $J$ = 9.0 Hz, 2H, H-3, H-5 Ar), 7.91(d, $J$ = 9.0 Hz, 2H, H-2, H-6 Ar), 7.34 (s, 1H, H-5), 4.12 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.05 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.9, 164.5, 160.1, 148.7, 147.8, 146.6, 142.4, 127.5, 124.8, 121.4, 116.1, 63.2, 13.3; IR (ATR): 3085, 1720, 1630, 1526, 1351, 1251, 1123, 1068, 867, 802, 758 cm$^{-1}$; Anal. calcd for $C_{15}H_{15}N_2O_7 \cdot 0.25H_2O$: C, 53.50; H, 3.74; N, 8.32; found: C, 53.58; H, 3.61; N, 8.34.

**1-(4-Bromophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10h).**



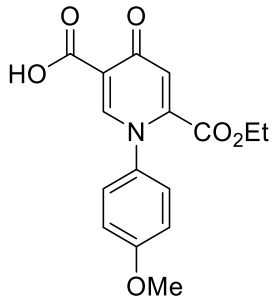
Yield 59% (0.065 g), beige solid, mp 226–227 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.26 (s, 1H, OH), 8.59 (s, 1H, H-2), 7.78 (d, $J$ = 8.8 Hz, 2H, Ar), 7.57 (d, $J$ = 8.8 Hz, 2H, Ar), 7.27 (s, 1H, H-5), 4.11 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.02 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 164.7, 160.2, 148.6, 143.1, 140.9, 132.5, 127.9, 123.0, 120.7, 116.0, 63.0, 13.2; IR (ATR): 3055, 2997, 1710, 1627, 1527, 1465, 1278, 1065, 1010, 866, 802, 677 cm$^{-1}$; Anal. calcd for $C_{15}H_{12}BrNO_5 \cdot 0.25H_2O$: C, 48.61; H, 3.40; N, 3.78; found: C, 48.81; H, 3.31; N, 3.67.

**6-(Ethoxycarbonyl)-4-oxo-1-(p-tolyl)-1,4-dihydropyridine-3-carboxylic acid (10i).**



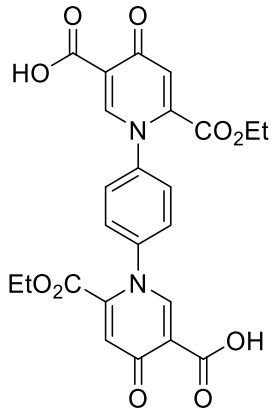
Yield 76% (0.069 g), beige solid, mp 184–185 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.35 (s, 1H, OH), 8.51 (s, 1H, H-2), 7.45 (d, $J$ = 8.3 Hz, 2H, Ar), 7.37 (d, $J$ = 8.3 Hz, 2H, Ar), 7.23 (s, 1H, H-5), 4.08 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.39 (s, 3H, Me-Ar), 0.98 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.6, 164.8, 160.4, 148.4, 143.9, 139.7, 139.1, 130.0, 125.2, 120.1, 115.9, 62.9, 20.6, 13.2; IR (ATR): 3093, 2967, 2928, 1729, 1627, 1525, 1464, 1179, 1113, 1014, 973, 845, 809 cm$^{-1}$; Anal. calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65; found: C, 63.36; H, 5.42; N, 4.51.

**6-(Ethoxycarbonyl)-1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10j).**



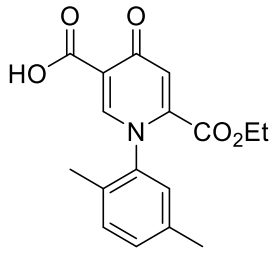
Yield 75% (0.072 g), beige solid, mp 203–204 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.40 (s, 1H, OH), 8.50 (s, 1H, H-2), 7.51 (d, $J$ = 9.1 Hz, 2H, H-2, H-6 Ar), 7.22 (s, 1H, H-5), 7.09 (d, $J$ = 9.1 Hz, 2H, H-3, H-5 Ar), 4.09 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.82 (s, 3H, OMe), 1.00 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.6, 164.8, 160.4, 160.0, 148.6, 144.2, 134.3, 126.9, 119.8, 115.8, 114.6, 62.8, 55.6, 13.3; IR (ATR): 3048, 3006, 2970, 2840, 1725, 1630, 1525, 1464, 1374, 1249, 1188, 1070, 1020, 919, 844, 803 cm$^{-1}$; Anal. calcd for $C_{16}H_{15}NO_6 \cdot 0.25H_2O$: C, 53.50; H, 3.74; N, 8.32; found: C, 53.58; H, 3.61; N, 8.34.

**1,1'-(1,4-Phenylene)bis(6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid) (10k).**



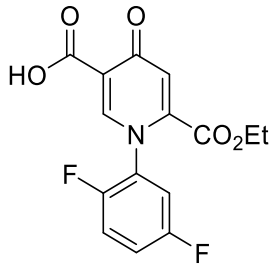
Yield 59% (0.044 g), beige solid, mp 275–276 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.18 (s, 2H, OH), 7.81 (s, 2H, H-2), 7.31 (s, 2H, H-5), 4.14 (q, $J$ = 7.1 Hz, 4H, $CH_2$), 1.12 (t, $J$ = 7.1 Hz, 6H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.8, 167.9, 164.7, 148.6, 143.0, 142.4, 127.1, 120.8, 119.3, 63.1, 13.4; IR (ATR): 3077, 2985, 2937, 1729, 1627, 1532, 1474, 1373, 1281, 1126, 1012, 857, 800, 778 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{24}H_{20}N_2O_2^+$ $(M+H)^+$ 497.1191, found: 497.1202.

**1-(2,5-Dimethylphenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10l).**



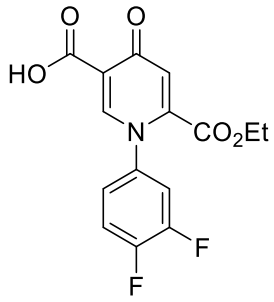
Yield 92% (0.086 g), beige solid, mp 123–124 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.32 (s, 1H, OH), 8.49 (s, 1H, H-2), 7.33–7.27 (m, 3H, Ar), 7.27 (s, 1H, H-5), 4.06 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.31 (s, 3H, Me-Ar), 2.07 (s, 3H, Me-Ar), 0.94 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.6, 164.7, 160.1, 148.2, 144.0, 140.1, 136.7, 130.9, 130.86, 130.82, 127.0, 120.0, 116.4, 62.8, 20.1, 16.3, 13.1; IR (ATR): 3055, 2986, 1720, 1627, 1525, 1456, 1369, 1201, 1010, 802, 772 cm$^{-1}$; Anal. calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44; found: C, 65.17; H, 5.83; N, 4.89.

**1-(2,5-Difluorophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10m).**



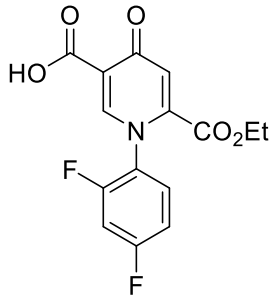
Yield 59% (0.058 g), beige solid, mp 124–125 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 14.93 (s, 1H, OH), 8.78 (s, 1H, H-2), 7.83 (ddd, $J$ = 8.9 Hz, $J$ = 6.0 Hz, $J$ = 3.0 Hz, 1H, H-6 Ph), 7.61–7.43 (m, 2H, Ar), 7.34 (s, 1H, H-5), 4.18 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.10 (q, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 46.36–46.36 (m, 1F), 33.56–33.42 (m, 1F); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.8, 164.2, 159.7, 157.5 (dd, $J$ = 243.2 Hz, $J$ = 2.3 Hz, C-F), 152.7 (dd, $J$ = 245.4 Hz, $J$ = 3.1 Hz, C-F), 149.5, 142.3, 129. 4 (dd, $J$ = 15.2 Hz, $J$ = 11.4 Hz), 121.4, 118.6 (dd, $J$ = 24.1 Hz, $J$ = 8.2 Hz), 117.5 (dd, $J$ = 22.2 Hz, $J$ = 9.3 Hz), 116.6, 115.6 (d, $J$ = 27.5 Hz), 63.1, 13.2; IR (ATR): 3070, 2988, 1717, 1635, 1505, 1433, 1251, 1175, 1112, 1061, 887, 802, 768 cm$^{-1}$; Anal. calcd for $C_{15}H_{11}F_2NO_5$: C, 55.74; H, 3.43; N, 4.33; found: C, 55.33; H, 3.45; N, 4.46.

**1-(3,4-Difluorophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10n).**



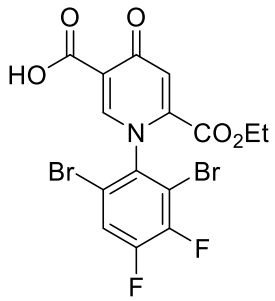
Yield 70% (0.068 g), beige solid, mp 176–177 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.20 (s, 1H, OH), 8.64 (s, 1H, H-2), 7.96 (ddd, $J$ = 10.9 Hz, $J$ = 7.0 Hz, $J$ = 2.6 Hz, 1H, H-2 Ar), 7.66 (dt, $J$ = 10.4 Hz, $J$ = 8.8 Hz, 1H, H-4 Ar), 7.55–7.47 (m, 1H, H-5 Ar), 7.29 (s, 1H, H-5), 4.13 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.06 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (471 MHz, DMSO-$d_6$) δ 26.71 (dddd, $J$ = 22.1 Hz, $J$ = 10.2 Hz, $J$ = 9.1 Hz, $J$ = 1.6 Hz), 26.22 (dddd, $J$ = 22.1 Hz, $J$ = 10.5 Hz, $J$ = 7.0 Hz, $J$ = 3.8 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 164.5, 160.0, 149.9 (dd, $J$ = 246.6 Hz, $J$ = 11.5 Hz), 149.0 (dd, $J$ = 246.6 Hz, $J$ = 11.5 Hz), 148.9, 142.9, 137.8 (dd, $J$ = 8.8 Hz, $J$ = 3.5 Hz), 123.6 (dd, $J$ = 7.3 Hz, $J$ = 3.6 Hz), 120.7, 118.0 (d, $J$ = 18.7 Hz), 116.5 (d, $J$ = 20.5 Hz), 116.0, 63.0, 13.2; IR (ATR): 3060, 2990, 2946, 1713, 1635, 1467, 1515, 1371, 1218, 1124, 876, 801 cm$^{-1}$; Anal. calcd for $C_{15}H_{11}F_2NO_5$: C, 55.74; H, 3.43; N, 4.33; found: C, 55.12; H, 3.45; N, 4.22.

**1-(2,4-Difluorophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10o).**



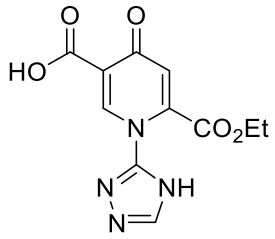
Yield 69% (0.067 g), beige solid, mp 178–179 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.00 (s, 1H, OH), 8.75 (s, 1H, H-2), 7.83 (td, $J$ = 8.9 Hz, $J$ = 5.8 Hz, 1H, Ar), 7.60 (ddd, $J$ = 10.6 Hz, $J$ = 9.0 Hz, $J$ = 2.8 Hz, 1H, Ar), 7.32 (s, 1H, H-5), 7.32–7.27 (m, 1H, Ar), 4.16 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.09 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ 56.20 (qd, $J$ = 8.5 Hz, $J$ = 5.8 Hz), 43.90 (q, $J$ = 9.4 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.8, 164.3, 162.7 (dd, $J$ = 250.0 Hz, $J$ = 11.7 Hz, C-F), 159.8, 156.5 (dd, $J$ = 251.7 Hz, $J$ = 13.5 Hz, C-F), 149.6, 142.7, 129.6 (d, $J$ = 10.6 Hz), 125.7 (dd, $J$ = 13.1 Hz, $J$ = 4.1 Hz), 121.2, 116.6, 112.3 (dd, $J$ = 23.1 Hz, $J$ = 3.7 Hz), 105.0 (dd, $J$ = 27.7 Hz, $J$ = 23.5 Hz), 63.1, 13.3; IR (ATR): 3063, 2992, 1720, 1628, 1482, 1249, 1218, 1122, 1063, 960, 865, 802 cm$^{-1}$; Anal. calcd for $C_{15}H_{11}F_2NO_5$: C, 55.74; H, 3.43; N, 4.33; found: C, 55.42; H, 3.40; N, 4.48.

**1-(2,6-Dibromo-4,5-difluorophenyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10p).**



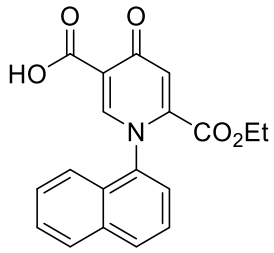
Yield 84% (0.10 g), beige solid, mp 174–175 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 14.65 (s, 1H, OH), 8.89 (s, 1H, H-2), 8.32 (dd, $J$ = 9.8 Hz, $J$ = 7.8 Hz, 1H, Ar), 7.46 (s, 1H, H-5), 4.21 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.15 (t, $J$ = 7.1 Hz, 3H, Me); $^{19}$F NMR (471 MHz, DMSO-$d_6$) δ 35.30 (dd, $J$ = 23.4 Hz, $J$ = 7.7 Hz), 32.36 (dd, $J$ = 23.4 Hz, $J$ = 9.8 Hz); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 163.9, 159.1, 150.0 (dd, $J$ = 257.2 Hz, $J$ = 14.6 Hz, C-F), 149.1, 147.0 (dd, $J$ = 248.3 Hz, $J$ = 14.9 Hz, C-F), 141.2, 136.2 (d, $J$ = 4.2 Hz), 122.2, 120.8 (d, $J$ = 21.6 Hz), 117.8, 117.0 (dd, $J$ = 9.1 Hz, $J$ = 4.4 Hz), 112.4 (d, $J$ = 20.6 Hz), 63.4, 13.3; IR (ATR): 3050, 1714, 1635, 1557, 1412, 1285, 1209, 1105, 860, 714 cm$^{-1}$; Anal. calcd for $C_{15}H_9Br_2F_2NO_5$: C, 37.45; H, 1.89; N, 2.91; found: C, 37.18; H, 1.76; N, 2.93.

**6-(Ethoxycarbonyl)-4-oxo-1-(4*H*-1,2,4-triazol-3-yl)-1,4-dihydropyridine-3-carboxylic acid (10q).**



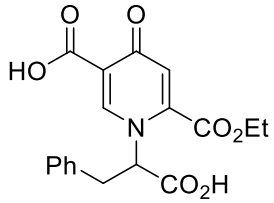
Yield 77% (0.064 g), beige solid, mp 207–208 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 14.73 (s, 1H, OH), 8.84 (s, 1H, CH), 8.79 (s, 1H, H-2), 7.19 (s, 1H, H-5), 4.22 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.14 (t, $J$ = 7.1 Hz, 3H, Me), the NH proton was not observed; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 179.1, 164.3, 160.5, 157.0, 145.9, 145.4, 142.1, 120.4, 116.5, 63.0, 13.4; IR (ATR): 3231, 3128, 2982, 1720, 1635, 1520, 1436, 1271, 1113, 1035, 941, 797 cm$^{-1}$; Anal. calcd for $C_{11}H_{10}N_4O_5$: C, 47.49; H, 3.62; N, 20.14; found: C, 47.68; H, 3.69; N, 20.38. HRMS(ESI): m/z calcd for $C_{11}H_{10}N_4O_5K^+$ $(M+K)^+$ 317.0283, found: 317.0285.

**6-(Ethoxycarbonyl)-1-(naphthalen-1-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10r).**



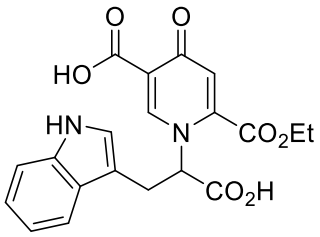
Yield 71% (0.072 g), beige solid, mp 174–175 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.34 (s, 1H, OH), 8.65 (s, 1H, H-2), 8.18 (dt, $J$ = 8.4 Hz, $J$ = 1.1 Hz, 1H, Naph), 8.15–8.09 (m, 1H, Naph), 7.80 (dd, $J$ = 7.3 Hz, $J$ = 1.1 Hz, 1H, Naph), 7.70–7.61 (m, 3H, Naph), 7.58 (d, $J$ = 8.1 Hz, 1H, Naph), 7.36 (s, 1H, H-5), 3.84 (qd, $J$ = 7.1 Hz, $J$ = 1.1 Hz, 2H, $CH_2$), 0.61 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.9, 164.7, 160.0, 149.0, 144.2, 137.5, 133.5, 130.5, 128.6, 128.4, 128.2, 127.2, 125.4, 124.9, 121.5, 120.6, 116.5, 62.6, 12.8; IR (ATR): 3077, 2983, 1735, 1629, 1532, 1466, 1392, 1266, 1106, 1001, 857, 849, 794 cm$^{-1}$; Anal. calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15; found: C, 67.24; H, 4.46; N, 4.34.

**1-(1-Carboxy-2-phenylethyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (11a).**



The product was recrystallized from EtOH. Yield 75% (0.081 g), mp 164–165 °C, beige solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 15.18 (s, 1H, OH), 13.98 (br.s, 1H, OH), 8.58 (s, 1H, H-2), 7.26–7.21 (m, 2H, H-3, H-5 Ph), 7.21–7.16 (m, 1H, H-4 Ph), 7.12 (d, $J$ = 7.6 Hz, 2H, H-2, H-6 Ph),7.06 (s, 1H, H-5), 5.84 (dd, $J$ = 10.5 Hz, $J$ = 5.3 Hz 1H, CH), 4.40–4.17 (m, 2H, $ABX_3$, $CH_2$), 3.61 (dd, $J$ = 14.5 Hz, $J$ = 5.3 Hz, 1H, C*H*H), 3.53 (dd, $J$ = 14.5 Hz, $J$ = 10.5 Hz, 1H, CH*H*), 1.29 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.9, 168.9, 164.6, 160.9, 148.1, 143.5, 136.0, 128.9, 128.5, 126.9, 120.6, 115.6, 68.0, 63.3, 37.5, 13.5; IR (ATR): 3059, 2984, 2937, 2568, 1735, 1628, 1515, 1477, 1372, 1249, 1211, 1154, 1126, 1052, 993, 871, 798 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{18}H_{17}NO_7Na^+$ $(M+Na)^+$ 382.0899, found: 382.0897.

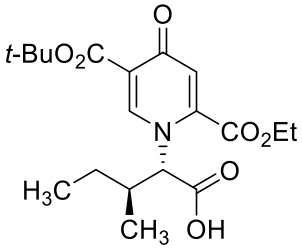
**1-(1-Carboxy-2-(3a*H*-indol-3-yl)ethyl)-6-(ethoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (11b).**



Yield 33% (0.039 g), mp 183–184 °C, beige solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 15.22 (s, 1H, OH), 10.90 (d, $J$ = 2.4 Hz, 1H, NH), 8.59 (s, 1H, H-2), 7.39 (d, $J$ = 7.9 Hz, 1H, Ind), 7.30 (dt, $J$ = 7.9 Hz, $J$ = 1.0 Hz, 1H, Ind), 7.05 (ddd, $J$ = 8.2 Hz, $J$ = 7.0, $J$ = 1.2 Hz, 1H, Ind), 6.99 (d, $J$ = 2.4 Hz, 1H, H-2 Ind), 6.94 (ddd, $J$ = 8.0 Hz, $J$ = 7.0 Hz, $J$ = 1.0 Hz, 1H, Ind), 6.92 (s, 1H, H-5), 5.82 (dd, $J$ = 9.5 Hz, $J$ = 5.5 Hz, 1H, CH), 4.16 (dd, $J$ = 10.6 Hz, $J$ = 5.5 Hz, 1H, C*H*H), 3.92 (br.s, 1H, CH*H*), 3.70–3.55 (m, 2H, $CH_2$Me), 1.16 (t, $J$ = 7.0 Hz, 3H, Me), the OH group was not observed due to broadening; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.9, 169.4, 164.5, 160.7, 148.0, 143.2, 136.1, 126.3, 124.4, 121.2, 120.6, 118.6, 117.5, 115.8, 111.5, 111.5, 107.5, 63.2, 27.8, 13.3; IR (ATR): 3423, 2996, 1726, 1627, 1486, 1422, 1342, 1271, 1231, 1157, 1070, 1052, 1011, 829 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{20}H_{18}N_2O_7Na^+$ $(M+Na)^+$ 421.1006, found: 421.1021.

**(2*S*,3*S*)-2-(5-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-oxopyridin-1(4*H*)-yl)-3-methylpentanoic acid** (**11c**).

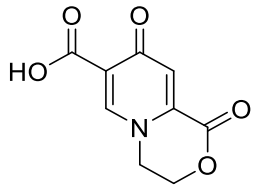
Diketonate **2a** (0.100 g, 0.30 mmol) and L-isoleucine (0.043 g, 0.33 mmol) were stirred in AcOH (1 mL) for 3 days at room temperature. The solvent was evaporated in an evaporation dish. Compound was isolated by extraction with EtOAc (3x2 mL). The combined organic layers were washed with water (3 mL), brine (3 mL) and dried with $MgSO_4$. The substance was purified by flash chromatography with the use of EtOH as an eluent.



Yield 70% (0.077 g), mp 183–184 °C, beige solid. $[\alpha]_D^{20}$ +71.9 (*c* 1.0, EtOH). $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.59 (s, 1H, H-2), 6.42 (s, 1H, H-5), 4.32–4.27 (m, ABX$_3$, 2H, $CH_2$Me), 4.24 (d, $J$ = 8.7 Hz, 1H, CHN), 2.04–1.93 (CHMe), 1.47 (s, 9H, *t*-Bu), 1.30 (t, $J$ = 7.1 Hz, 3H, Me), 0.91 (d, $J$ = 6.6 Hz, 3H, MeCH), 0.80 (t, $J$ = 7.3 Hz, 3H, Me), the OH group was not observed due to broadening; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 173.7, 169.9, 164.0, 162.6, 146.6, 143.2,

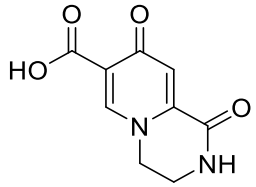
121.8, 119.5, 80.7, 72.1, 63.1, 38.1, 28.3, 25.4, 16.5, 14.1, 11.7. HRMS(ESI): m/z calcd for $C_{19}H_{28}NO_7^+$ $(M+H)^+$ 382.1860, found: 382.1865.

**1,8-Dioxo-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-7-carboxylic acid (12a).**



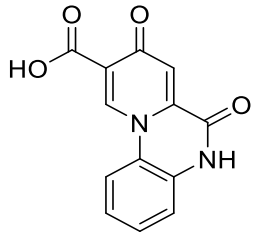
Yield 90% (0.079 g), beige solid, mp 292–293 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.75 (s, 1H, OH), 8.91 (s, 1H, H-6), 7.31 (s, 1H, H-9), 4.86–4.72 (m, 2H, $CH_2$), 4.56 (t, $J$ = 4.9 Hz, 2H, $CH_2$); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.6, 165.1, 157.8, 146.5, 138.4, 121.0, 116.4, 65.7, 48.4; IR (ATR): 3064, 2950, 1703, 1644, 1397, 1272, 1126, 992, 930, 803 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_9H_6NO_5^-$ $(M-H)^-$ 208.0246, found: 208.0269.

**1,8-Dioxo-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-7-carboxylic acid (12b).**



Yield 65% (0.040 g), beige solid, mp 280–281 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 16.02 (s, 1H, OH), 9.03 (s, 1H, NH), 8.84 (s, 1H, H-6), 7.18 (s, 1H, H-9), 4.52–4.36 (m, 2H, $CH_2$, H-4), 3.67–3.51 (m, 2H, $CH_2$, H-3); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 165.5, 157.2, 146.6, 142.3, 118.1, 115.8, 49.9, 37.5; IR (ATR): 3261, 3135, 3055, 1690, 1639, 1487, 1351, 1294, 1178, 1104, 956, 802 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_9H_9N_2O_4^+$ $(M+H)^+$ 209.0557, found: 209.0552.

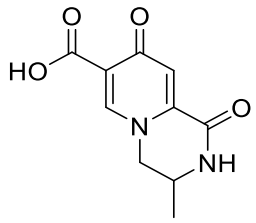
**6,8-Dioxo-6,8-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-9-carboxylic acid (12c).**



Yield 58% (0.044 g), beige solid, mp >350 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.86 (s, 1H, OH), 12.32 (s, 1H, NH), 9.57 (s, 1H, H-10), 8.39 (dd, $J$ = 8.1 Hz, $J$ = 1.7 Hz, 1H, H-1), 7.53 (s,

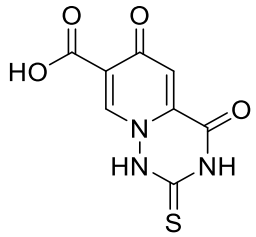
1H, H-7), 7.50 (td, $J$ = 7.5 Hz, $J$ = 1.0 Hz, 1H, H-3), 7.36–7.32 (m, 2H, Ar); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.8, 164.9, 153.9, 139.9, 138.4, 128.8, 128.3, 124.0, 122.6, 118.0, 117.2, 117.0, 116.5; IR (ATR): 3000, 2864, 2783, 1720, 1683, 1635, 1494, 1362, 1295, 1137, 1066, 929, 851, 797 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{13}H_7N_2O_4^-$ $(M-H)^-$ 255.0406, found: 255.0427.

**3-Methyl-1,8-dioxo-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-7-carboxylic acid (12d).**




Yield 84% (0.056 g), beige solid, mp 131–132 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.09 (s, 1H, NH), 8.74 (s, 1H, H-6), 7.15 (s, 1H, H-9), 4.48 (dd, $J$ = 13.0 Hz, $J$ = 3.6 Hz, 2H, H-4), 4.10 (dd, $J$ = 12.9 Hz, $J$ = 9.0 Hz, 1H, H-4), 4.00–3.93 (m, 1H, H-3), 1.18 (d, $J$ = 6.6 Hz, 3H, Me), the OH group was not observed due to broadening; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 178.7, 172.6, 165.5, 157.1, 146.5, 141.4, 118.2, 55.1, 44.2, 17.6; IR (ATR): 3258, 3121, 3048, 1690, 1639, 1483, 1345, 1294, 1212, 1182, 1103, 945, 809 cm$^{-1}$; Anal. calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61; found: C, 54.20; H, 4.46; N, 12.34.

**4,6-Dioxo-2-thioxo-2,3,4,6-tetrahydro-1*H*-pyrido[2,1-*f*][1,2,4]triazine-7-carboxylic acid (12e).**



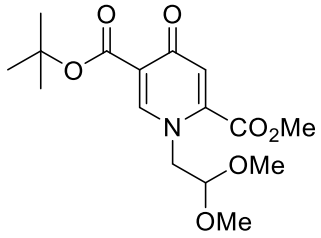

Yield 77% (0.064 g), yellow solid, mp 186–187 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.49 (s, 1H, H-8), 7.19 (s, 1H, H-5), the OH and 2NH were not observed due to broadening; $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 174.4, 168.1, 165.7, 153.8, 139.4, 136.7, 117.9, 113.5; IR (ATR): 3054, 2141, 1700, 1640, 1527, 1483, 1394, 1339, 1137, 1111, 995, 836 cm$^{-1}$; Anal. calcd for $C_8H_5N_3O_4S \cdot 2H_2O$: C, 34.91; H, 3.30; N, 15.27; found: C, 34.71; H, 3.03; N, 15.67; HRMS(ESI): m/z calcd for $C_8H_6N_3O_4S^+$ $(M+H)^+$ 240.0074, found: 240.0074.

**5-(*tert*-Butyl) 2-methyl 1-(2,2-dimethoxyethyl)-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (13).**

Diketonate **2b** (0.100 g, 0.300 mmol) and aminoacetaldehyde dimethyl acetal (0.035 g, 0.33 mmol) were added in AcOH (1 mL). The mixture was stirred for 24 h at room temperature. Then, the solvent was evaporated in an evaporation dish at room temperature. The residue was diluted with $H_2O$ (5 mL), the product was extracted with EtOAc (3x2 mL), the organic layer was washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated. Yield 81% (0.083 g), brown viscous liquid.

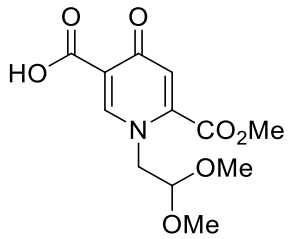
*Mechanoactivation*:

Diketonate **2b** (0.050 g, 0.15 mmol), 2,2-dimethoxyethan-1-amine (0.017 g, 0.165 mmol) and AcOH (0.45 mmol, 0.027g) were grinding in a mortar for 10 min. The residue was diluted with $H_2O$ (5 mL), the product was extracted with EtOAc (3x2 mL), the organic layer was washed with water brine, then was dried with anhydrous $MgSO_4$. The solvent was evaporated. Yield 82% (0.042 g), brown viscous liquid.




$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.23 (s, 1H, H-6), 6.60 (s, 1H, H-3), 4.51 (t, $J$ = 4.3 Hz, 1H, CH), 4.40 (d, $J$ = 4.3 Hz, 2H, $CH_2$), 3.85 (s, 3H, Me), 3.29 (s, 6H, 2MeO), 1.48 (s, 9H, *t*-Bu); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.5, 163.1, 162.5, 149.1, 140.6, 123.3, 120.3, 102.7, 80.5, 55.3, 54.1, 53.3, 27.8; IR (ATR): 2977, 2837, 1724, 1592, 1367, 1306, 1103, 1075, 1029, 796 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{16}H_{24}O_7^+$ $(M+H)^+$ 342.1548, found: 342.1561.

**1-(2,2-Dimethoxyethyl)-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (14).**



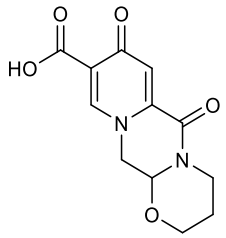

Diketonate **2b** (0.200 g, 0.62 mmol) and aminoacetaldehyde dimethyl acetal (0.072 g, 0.68 mmol) were stirred in AcOH (2 mL) acid at room temperature for 24 h and were refluxed for 6 h at 120 °C. After cooling, $H_2O$ (5 mL) was added, the product was extracted with EtOAc (3x2 mL). The

combined organic layers were washed with brine (2 mL) and were dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was recrystallized from toluene-hexane.

Yield 92% (0.162 g), brown solid, mp 134–135 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.75 (s, 1H, H-6), 7.11 (s, 1H, H-5), 4.64 (d, $J$ = 4.0 Hz, 2H, $CH_2N$), 4.59 (d, $J$ = 4.0 Hz, 1H, CH), 3.90 (s, 3H, Me), 3.30 (s, 6H, 2MeO), the OH group was not observed due to broadening; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.4, 165.0, 161.6, 150.4, 143.5, 121.0, 115.7, 102.2, 55.5, 55.2, 53.7; IR (ATR): 3055, 2953, 2845, 1735, 1630, 1375, 1201, 1163, 871, 800, 770 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{12}H_{16}NO_7^+$ $(M+H)^+$ 286.0922, found: 286.0926.

**6,8-Dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxylic acid (15).**

Compound **14** (0.040 g, 0.14 mmol) in MeCN were added $MeSO_3H$ (0.004 g, 0.04 mmol) and AcOH (0.050 g, 8.4 mmol), the mixture was heated at 65 °C for 4 h. After cooling to room temperature, 3-aminopropanol-1 (0.011 g, 0.14 mmol) was added. The reaction mixture was heated at 65 °C for 2 h. The solvent was evaporated in an evaporation dish. The residue was diluted with $H_2O$ (5 mL). The precipitate that formed was filtered and dried.



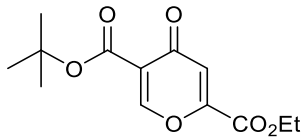

Yield 69% (0.025 g), beige solid, mp 297–298 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 15.81 (s, 1H, OH), 8.89 (s, 1H, H-10), 7.30 (s, 1H, H-7), 5.33 (t, $J$ = 3.9 Hz, 1H, H-12a), 4.63 (dd, $J$ = 14.3 Hz, $J$ = 3.9 Hz, 1H, H-12), 4.55 (dd, $J$ = 14.2 Hz, $J$ = 4.0 Hz, 1H, H-12), 4.48–4.40 (m, 1H, H-2), 4.08–4.03 (m, 1H, H-2), 3.89 (td, $J$ = 12.0 Hz, $J$ = 2.7 Hz, 1H, H-3), 3.24 (td, $J$ = 12.8 Hz, $J$ = 3.5 Hz, 1H, H-3), 1.84–1.67 (m, 1H, H-4), 1.62 (d, $J$ = 13.4 Hz, 1H, H-4); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.7, 165.2, 155.8, 146.9, 140.2, 118.8, 116.4, 81.1, 67.0, 51.1, 42.9, 24.8; IR (ATR): 3071, 2981, 2867, 1728, 1660, 1542, 1432, 1334, 1189, 1086, 968, 879, 802 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_{12}H_{12}N_2O_5Na^+$ $(M+Na)^+$ 287.0639, found: 287.0642.

**Synthesis of *tert*-butyl 4-oxo-4*H*-pyran-2-carboxylates 16**

The solution of diketonate **2** (3.0 mmol) in $CH_2Cl_2$ (10 mL) was treated with saturated $KHSO_4$ solution (0.20 g, 15.0 mmol) under 0 °C. The reaction mixture was stirred at 1 h under cooling and for 6 h for room temperature. The organic layer was separated, and the aqueous layer is further

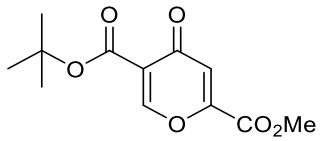
extracted with $CH_2Cl_2$ (5 mL). The organic layers were combined, washed with $H_2O$ (3 mL) and brine (3 mL), dried over anhydrous $Na_2SO_4$. The solvent was evaporated, and the product was recrystallized from hexane.

**5-(*tert*-Butyl) 2-ethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (16a).**



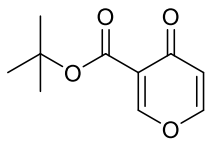

Yield 80% (0.437 g), yellowish solid, mp 68–69 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H, H-6), 7.16 (s, 1H, H-3), 4.43 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.56 (s, 9H, *t*-Bu), 1.40 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.6, 160.9, 160.5, 159.3, 151.9, 122.6, 121.7, 83.0, 63.2, 28.1, 14.0; IR (ATR): 3103, 2987, 1745, 1727, 1647, 1307, 1226, 1099, 940, 792 cm$^{-1}$; Anal. calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01; found: C, 58.37; H, 6.14.

**5-(*tert*-Butyl) 2-methyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (16b).**




Yield 56% (0.243 g), yellowish solid, mp 77–78 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, H-6), 7.15 (s, 1H, H-3), 3.98 (s, 3H, Me), 1.56 (s, 9H, *t*-Bu); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.5, 160.9, 160.4, 159.8, 151.7, 122.8, 121.9, 83.1, 53.7, 28.1; IR (ATR): 3086, 2960, 1727, 1651, 1574, 1413, 1306, 1227, 1149, 1099, 933, 885, 850 cm$^{-1}$; Anal. calcd for $C_8H_7O_6$: C, 56.69; H, 5.55; found: C, 56.40; H, 5.66.

***tert*-Butyl 4-oxo-4*H*-pyran-3-carboxylate (16c).**



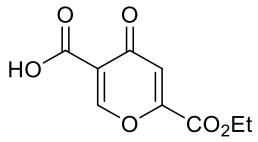

Yield 50% (0.341 g), yellowish solid, mp 88–89 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, $J$ = 1.1 Hz, 1H, H-6), 7.69 (dd, $J$ = 5.9 Hz, $J$ = 1.1 Hz, 1H, H-3), 6.43 (d, $J$ = 5.9 Hz, 1H, H-5), 1.56 (s, 9H, *t*-Bu); $^{13}$C (101 MHz, $CDCl_3$) δ 174.1, 161.3, 160.5, 154.1, 122.4, 119.9, 82.5, 28.1; IR

(ATR): 2976, 1735, 1617, 1384, 1362, 1284, 1237, 1055, 923, 884, 809 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_{10}H_{12}O_4Na^+$ $(M+Na)^+$ 219.0628; found: 219.0636. The NMR spectra is accordance with the literature data [1].

**Synthesis of 4-oxo-4*H*-pyran-3-carboxylic acids 17**

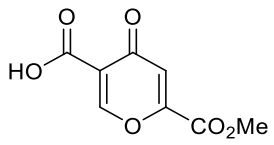
The solution of corresponding diketonate **2** (3.0 mmol) in $CH_2Cl_2$ (10 mL) was treated with $CF_3COOH$ (3.42 g, 30 mmol) under stirring while cooling on an ice bath. The reaction mixture was stirred for 1 h at 0 °C and for 4 h at room temperature. Then the resulting solution was treated with $H_2O$ (3x2 mL). The organic layer was separated, the aqueous layer was further extracted with $CH_2Cl_2$ (3x2 mL), the organic layers were combined, washed with $H_2O$ (3 mL) and brine (3 mL), dried with anhydrous $Na_2SO_4$. The solvent was evaporated, and the obtained acid was recrystallized from water with EtOH.

**6-(Ethoxycarbonyl)-4-oxo-4*H*-pyran-3-carboxylic acid (17a).**



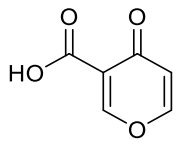

Yield 72% (0.458 g), beige solid, mp 122–123 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.29 (s, 1H, OH), 9.00 (s, 1H, H-2), 7.12 (s, 1H, H-5), 4.37 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.32 (t, $J$ = 7.1 Hz, 3H, Me); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 180.3, 163.1, 162.5, 159.2, 154.9, 119.8, 118.5, 64.0, 14.0; IR (ATR): 3077, 3000, 1748, 1640, 1236, 1151, 914, 812 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_9H_8O_6$ $(M+H)^+$ 213.0399; found: 213.0393.

**6-(Methoxycarbonyl)-4-oxo-4*H*-pyran-3-carboxylic acid (17b).**



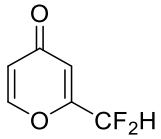

Yield 99% (0.588 g), beige solid, mp 145–146 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.29 (s, 1H, OH), 8.99 (s, 1H, H-2), 7.12 (s, 1H, H-5), 3.91 (s, 3H, Me); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.7, 160.1, 156.9, 152.7, 119.0, 117.8, 53.4, 34.4; IR (ATR): 3075, 2965, 1723, 1685, 1655, 1439, 1258, 1018, 877 $cm^{-1}$; HRMS(ESI): m/z calcd for $C_8H_6O_6$ $(M+H)^+$ 155.0349; found: 155.0337.

**4-Oxo-4*H*-pyran-3-carboxylic acid (17c).**



Yield 90% (0.378 g), beige solid, mp 178–179 °C. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 13.61 (s, 1H, OH), 9.00 (s, 1H, H-2), 8.44 (d, $J$ = 5.8 Hz, 1H, H-5), 6.73 (d, $J$ = 5.7 Hz, 1H, H-6); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 177.8, 163.5, 163.3, 158.7, 118.6, 117.6; IR (ATR): 3116, 2960, 1721, 1685, 1676, 1575, 1436, 1260, 979, 861 cm$^{-1}$; HRMS(ESI): m/z calcd for $C_6H_5O_4$ $(M+H)^+$ 141.0188, found: 141.0193.

**2-(Difluoromethyl)-4*H*-pyran-4-one.**



The solution of corresponding diketonate **2e** (0.100 g, 0.32 mmol) in $CH_2Cl_2$ (1 mL) was treated with $CF_3COOH$ (0.146 g 1.28 mmol) under stirring while cooling on an ice bath. The reaction mixture was stirred for 1 h at 0 °C and for 3 h at room temperature. The resulting solution was treated with $H_2O$ (3x2 mL). The organic layer was separated, the aqueous layer was further extracted with $CH_2Cl_2$ (3x2 mL). All organic layers were combined, washed with $H_2O$ (1 mL), a saturated $NaHCO_3$ solution (1 mL), brine (1 mL), dried with anhydrous $Na_2SO_4$. The solvent was evaporated.

Yield 80% (0.037 g), orange solid. Characterization data: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J$ = 5.8 Hz, 1H, H-6), 6.73 (d, $J$ = 2.4 Hz, 1H, H-3), 6.54 (d, $J$ = 5.8 Hz, $J$ = 2.4 Hz, 1H, H-5), 6.40 (t, $J$ = 53.5 Hz, 1H, $CF_2H$). The NMR spectrum is in accordance with the literature [4].

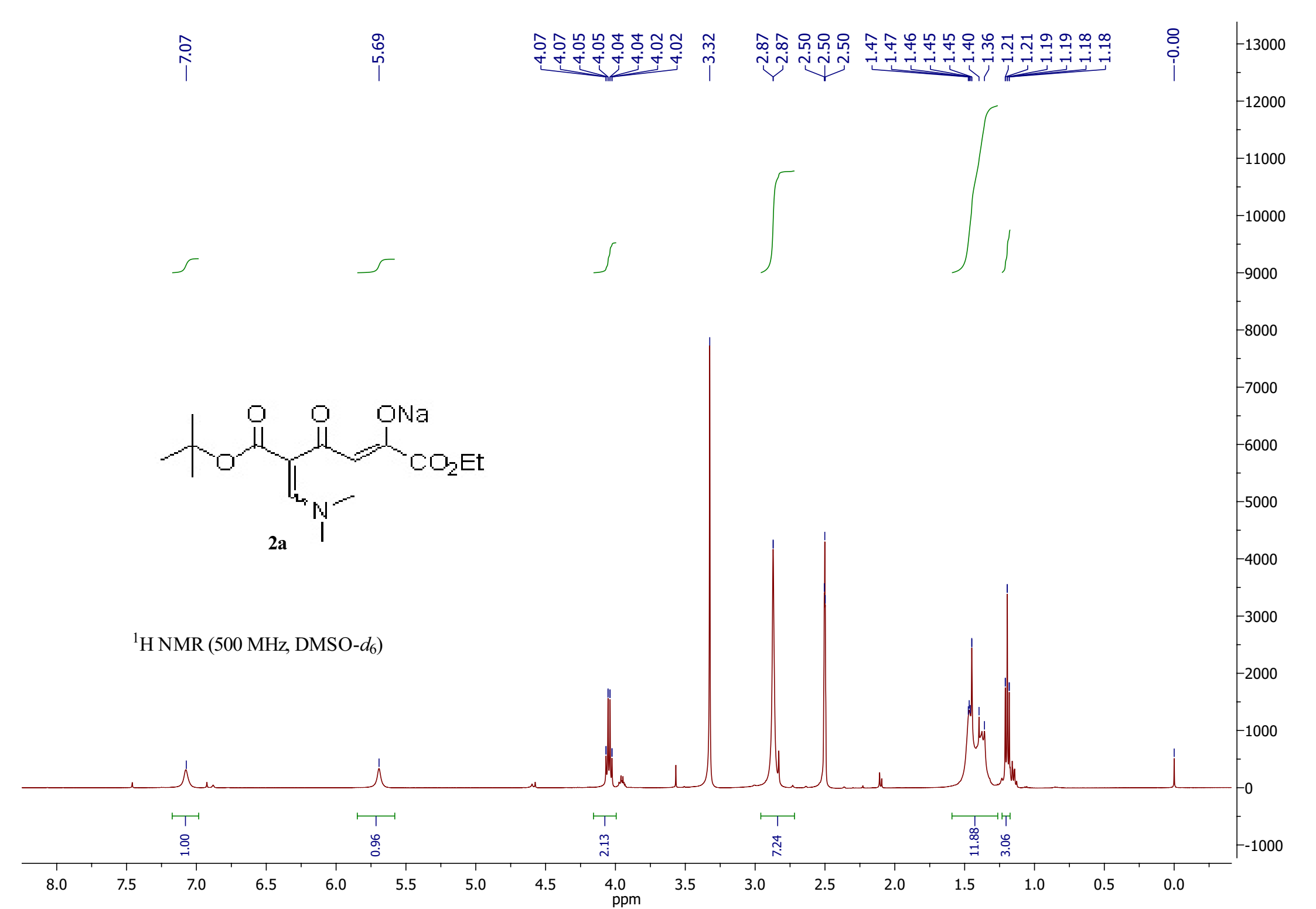
**References**

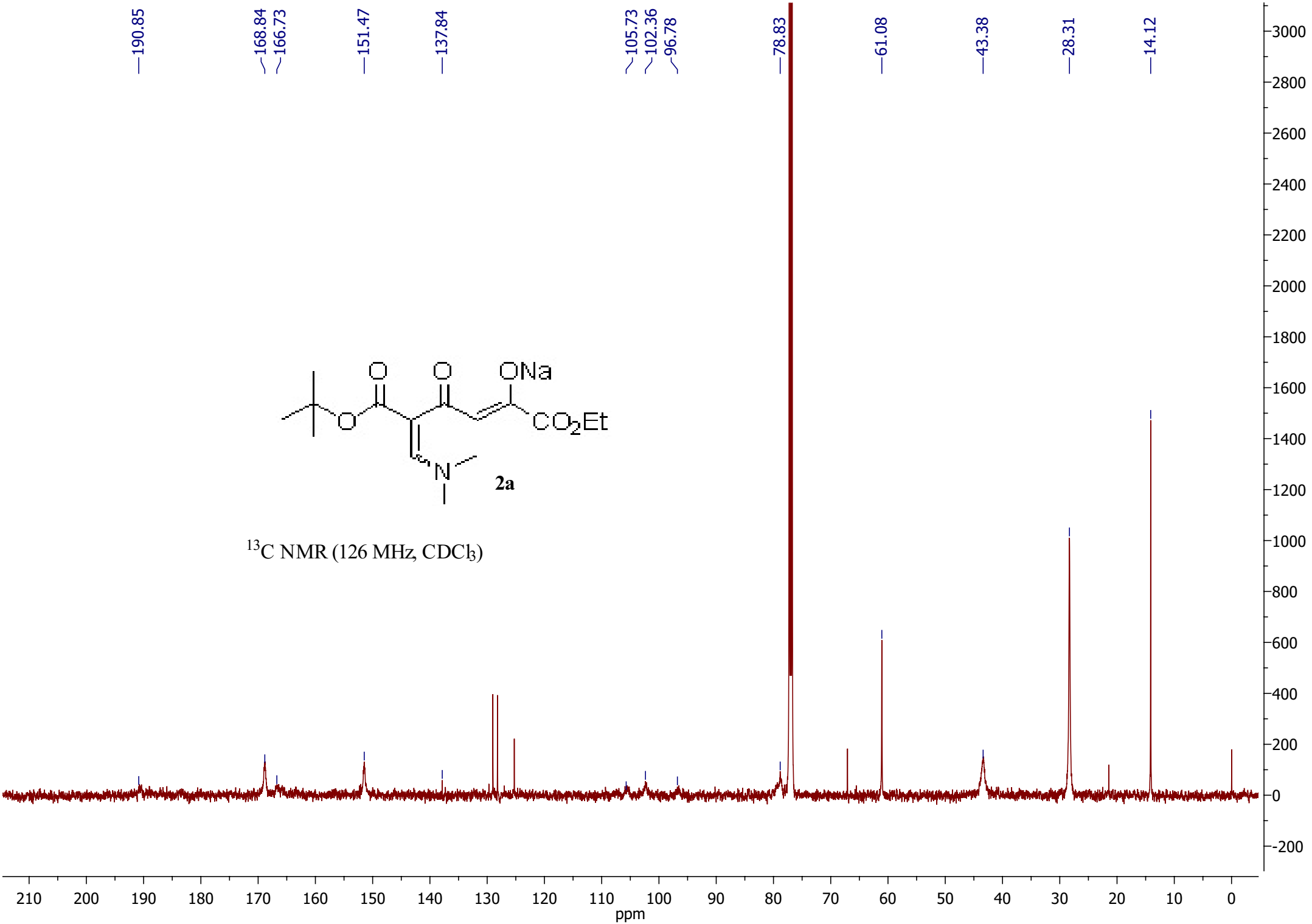
1. K. Nong, Y.-L. Zhao, S. Yi, X. Zhang, S. Wei and Z.-J. Yao, *Bioconjugate Chem.*, 2024, **35**, 286.

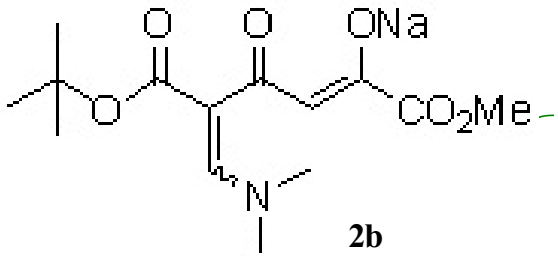
2. D. L. Obydennov, G-V. Röschenthaler and V. Y. Sosnovskikh, *Tetrahedron Letters*, 2013, 54, 6545.

3. Z. Li, Z. Wang, N. Chekshin, S. Qian, J. X. Qiao, P. T. Cheng, K.-S. Yeung, W. R. Ewing and J.-Q. Yu, *Science*, 2021, **372**, 1452.

4. B.I. Usachev, S.A. Usachev, G.-V. Röschenthaler and V.Y. Sosnovskikh, *Russian Chemical Bulletin*, 2010, **59**, 845.

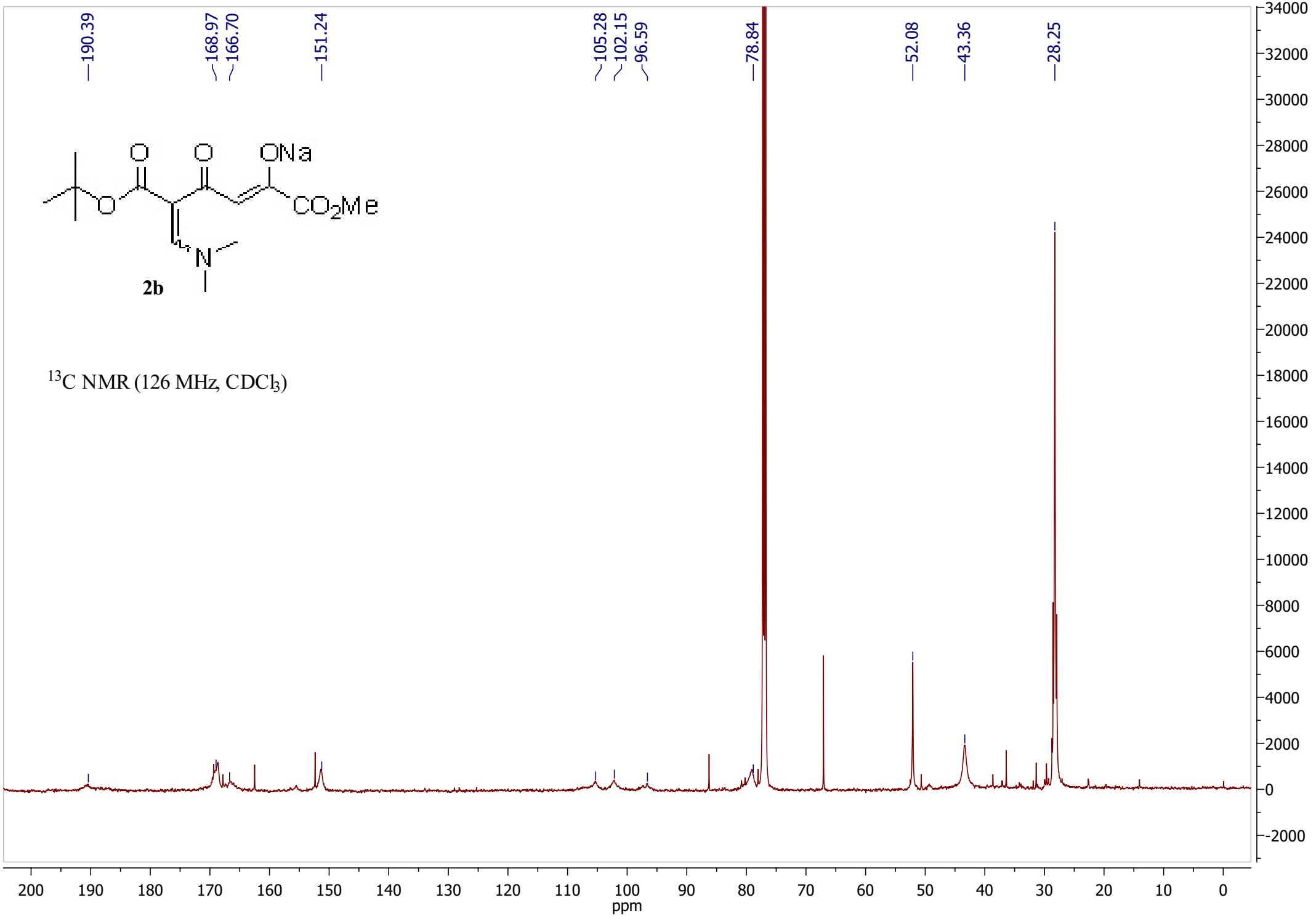

7.07
5.69
4.07
4.07
4.05
4.05
4.04
4.04
4.02
4.02
3.32
2.87
2.87
2.50
2.50
2.50
1.47
1.47
1.46
1.45
1.45
1.40
1.36
1.21
1.21
1.19
1.19
1.18
1.18
0.00
ONa
CO2Et
N
2a
1H NMR (500 MHz, DMSO-d6)
1.00
0.96
2.13
7.24
11.88
3.06
ppm

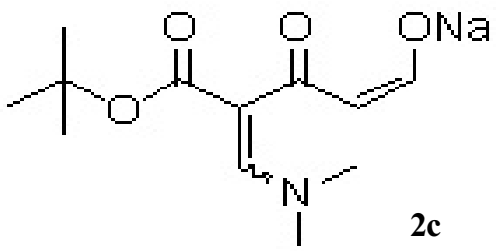

190.85
168.84
166.73
151.47
137.84
105.73
102.36
96.78
78.83
61.08
43.38
28.31
14.12
ONa
CO2Et
N
2a
13C NMR (126 MHz, CDCl3)
ppm




**2b**

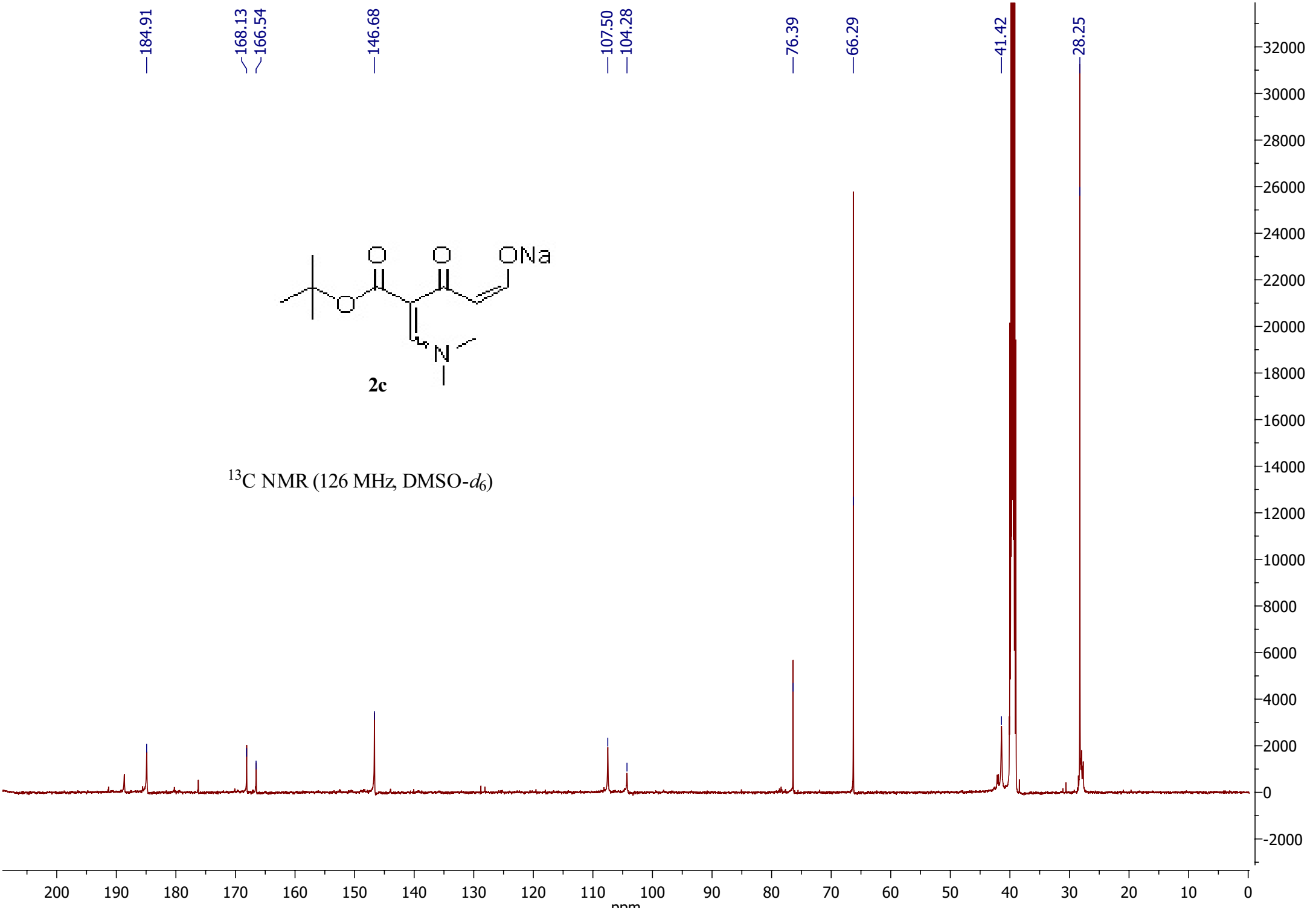
$^{1}$H NMR (500 MHz, $CDCl_3$)

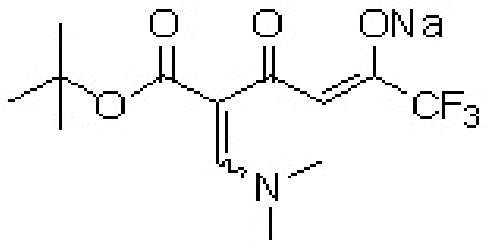

190.39
168.97
166.70
151.24
105.28
102.15
96.59
78.84
52.08
43.36
28.25
ONa
CO2Me
O
O
N
2b
13C NMR (126 MHz, CDCl3)
ppm




**2c**

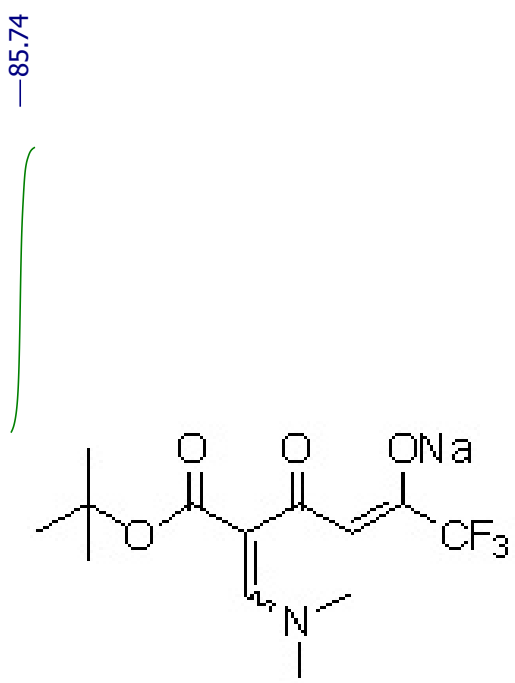
$^1$H NMR (400 MHz, DMSO-$d_6$)


184.91
168.13
166.54
146.68
107.50
104.28
76.39
66.29
41.42
28.25
ONa
N
2c
$^{13}$C NMR (126 MHz, DMSO-$d_6$)
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



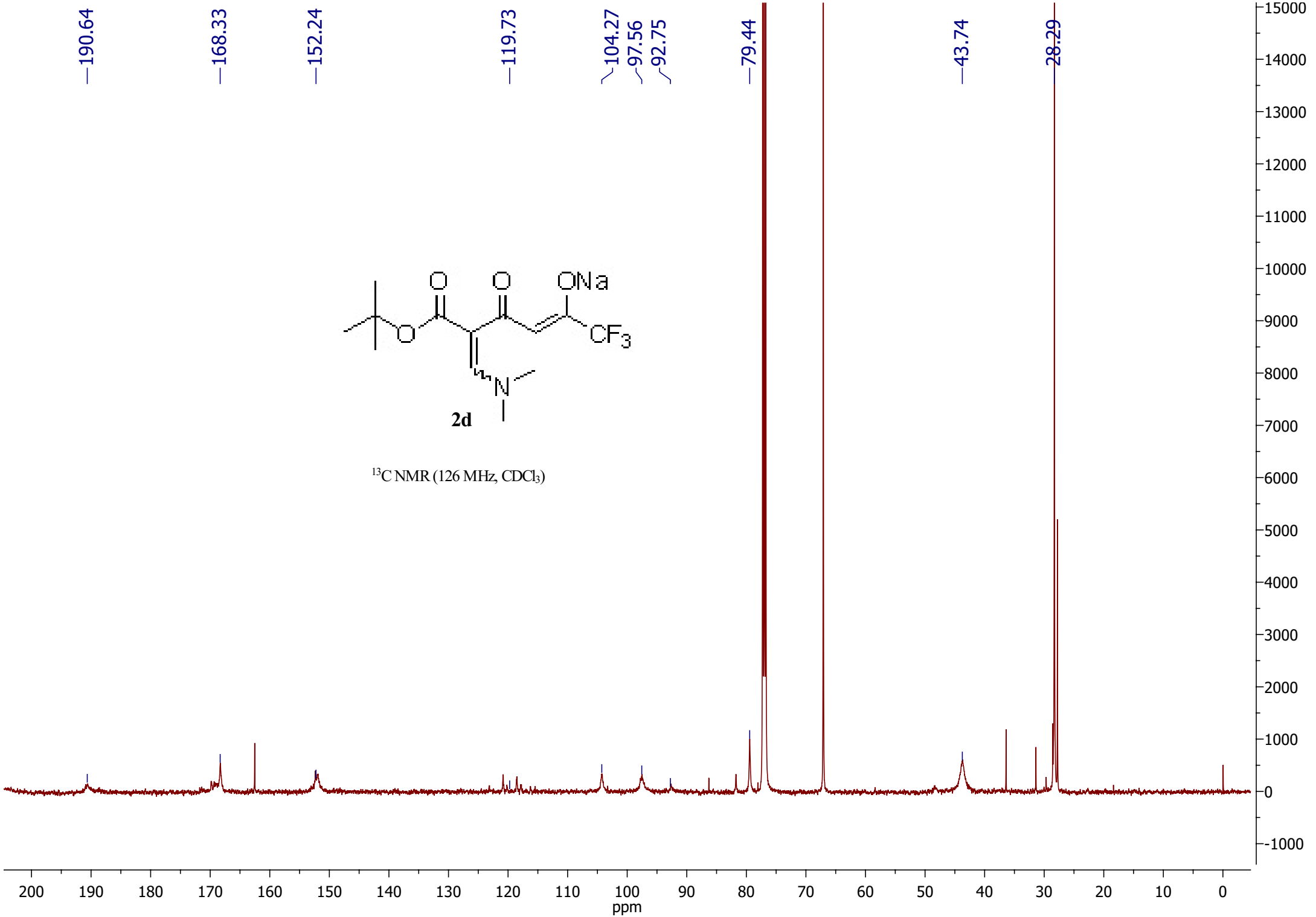

**2d**

$^{1}$H NMR (400 MHz, $CDCl_3$)




**2d**

$^{19}F$ NMR (376 MHz, $CDCl_3$)


190.64
168.33
152.24
119.73
104.27
97.56
92.75
79.44
43.74
28.29
ONa
O
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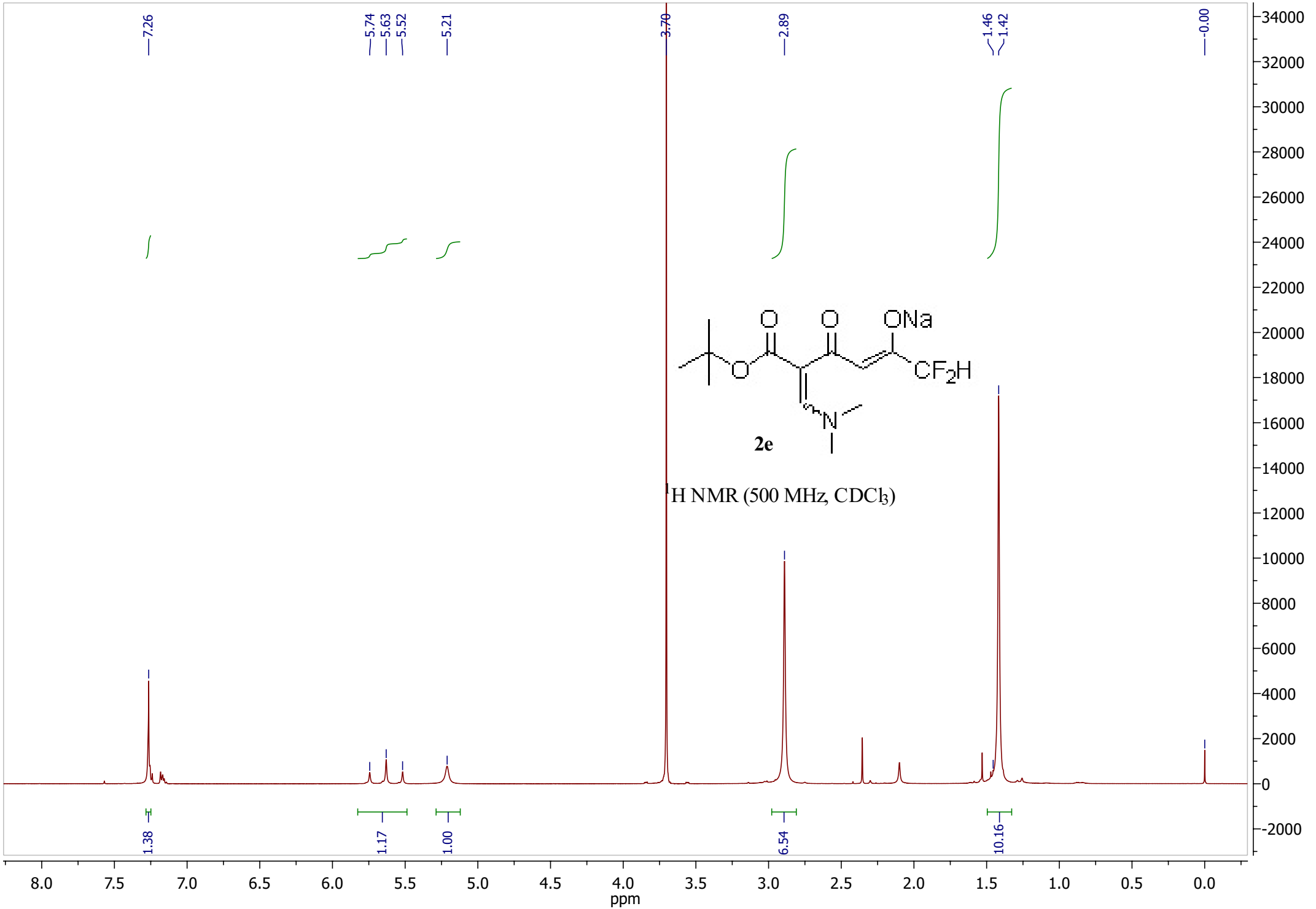
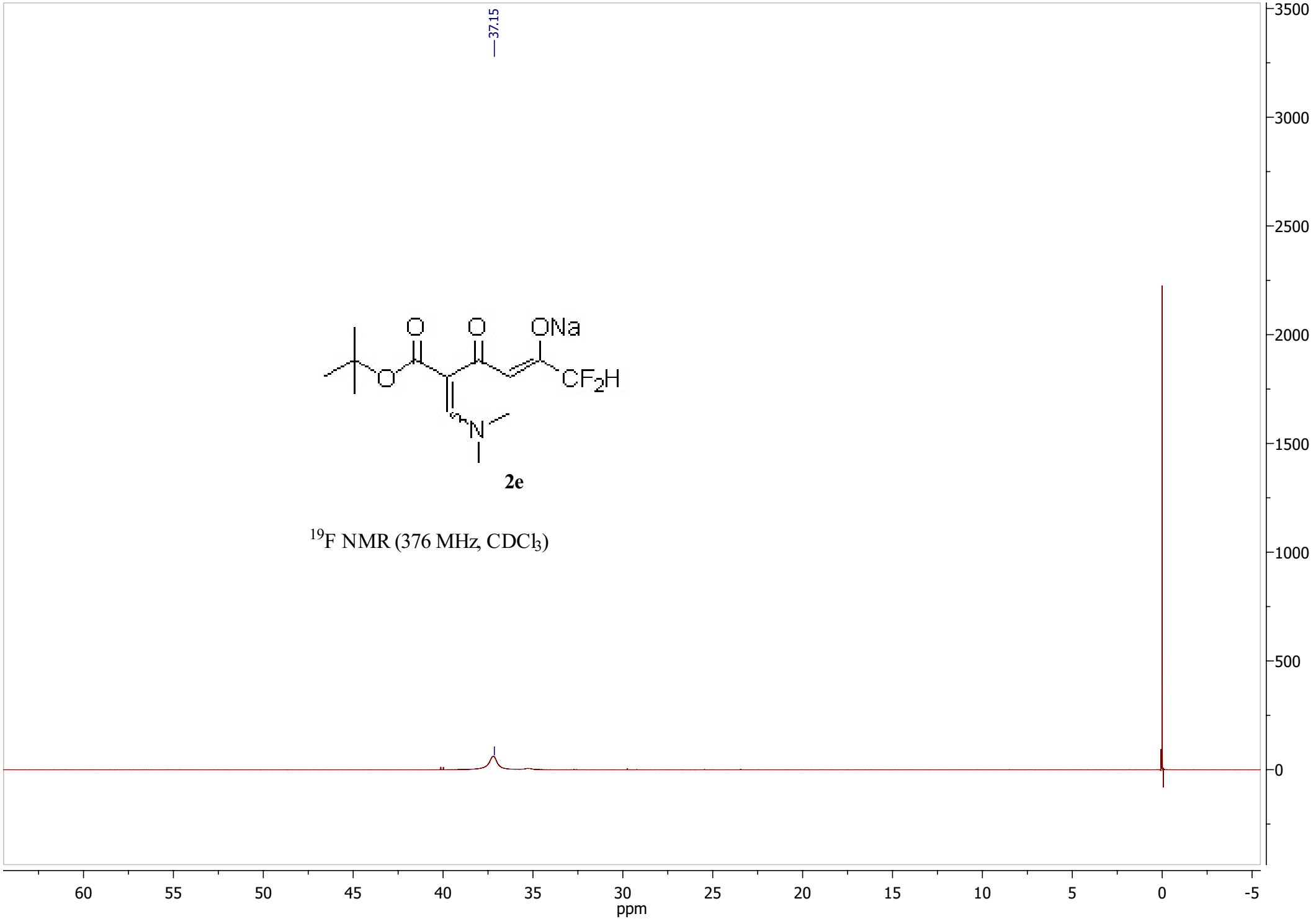
O
CF3
N
2d
13C NMR (126 MHz, CDCl3)
ppm


7.26
5.74
5.63
5.52
5.21
3.70
2.89
1.46
1.42
0.00
ONa
CF2H
2e
1H NMR (500 MHz, CDCl3)
1.38
1.17
1.00
6.54
10.16
ppm

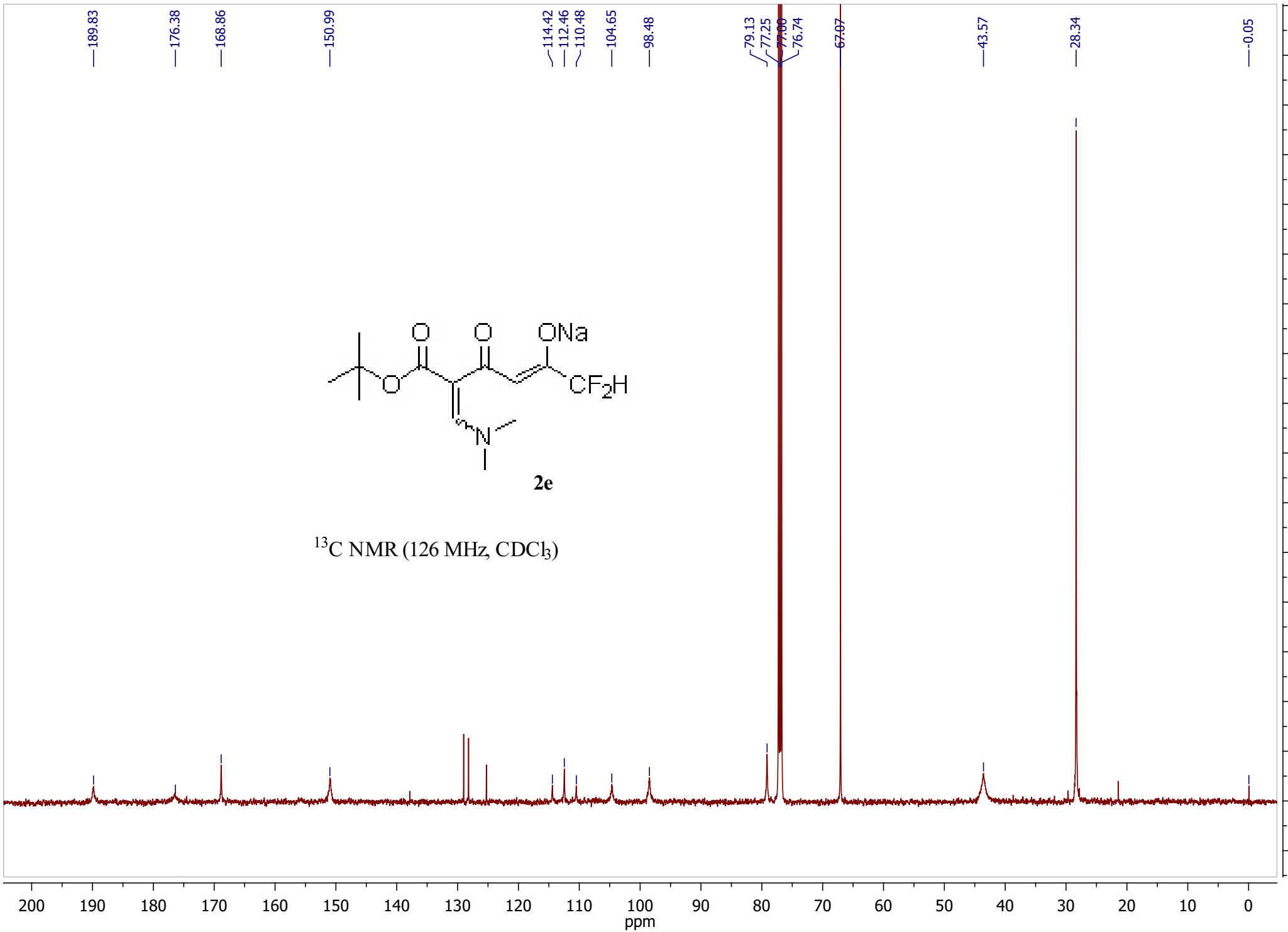


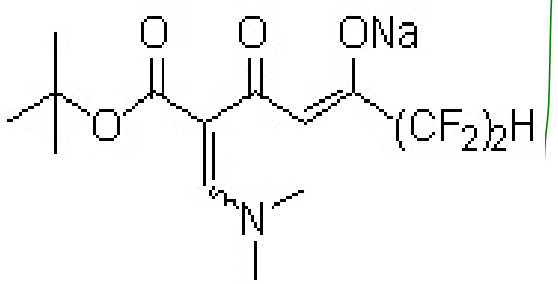




**2e**

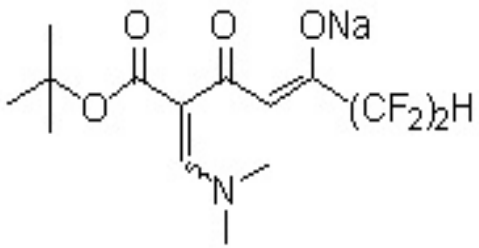
$^{19}F$ NMR (376 MHz, $CDCl_3$)


189.83
176.38
168.86
150.99
114.42
112.46
110.48
104.65
98.48
79.13
77.25
77.00
76.74
67.07
43.57
28.34
-0.05
ONa
O
O
O
CF2H
N
2e
13C NMR (126 MHz, CDCl3)
ppm



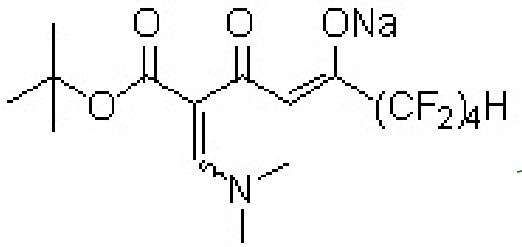

**2f**

$^{19}$F NMR (376 MHz, DMSO-$d_6$)



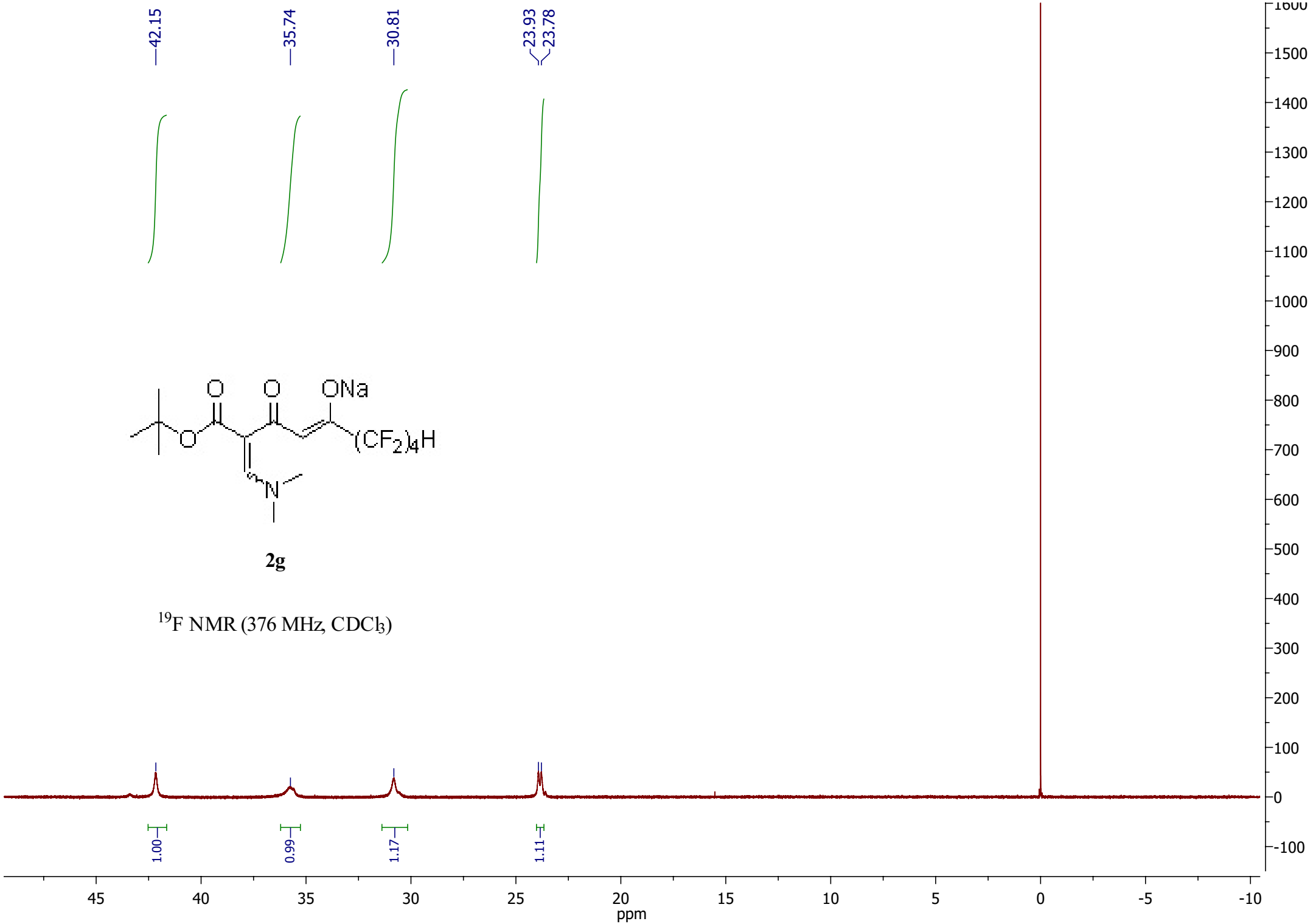
**2f**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



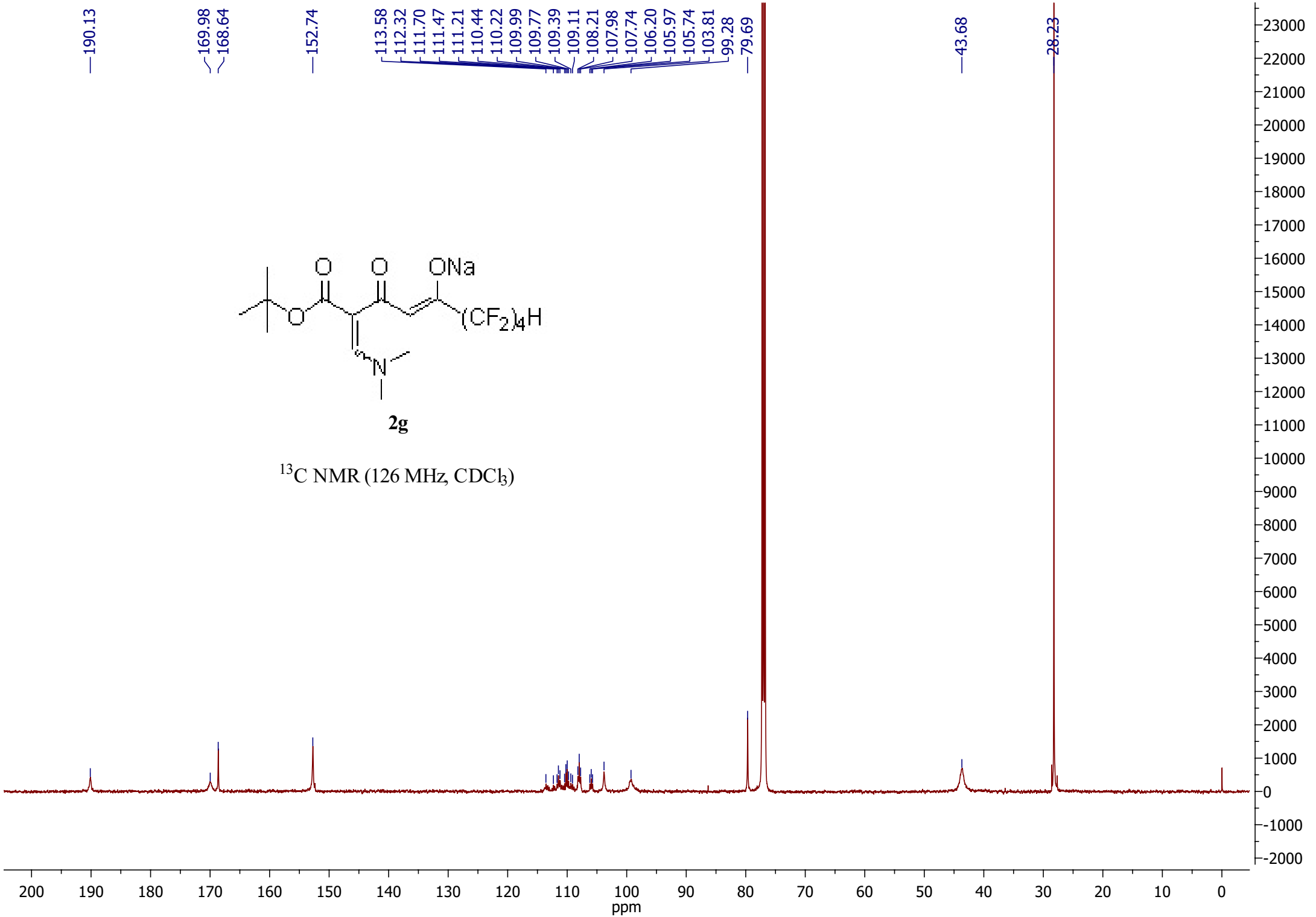

**2g**

$^1$H NMR (400 MHz, $CDCl_3$)



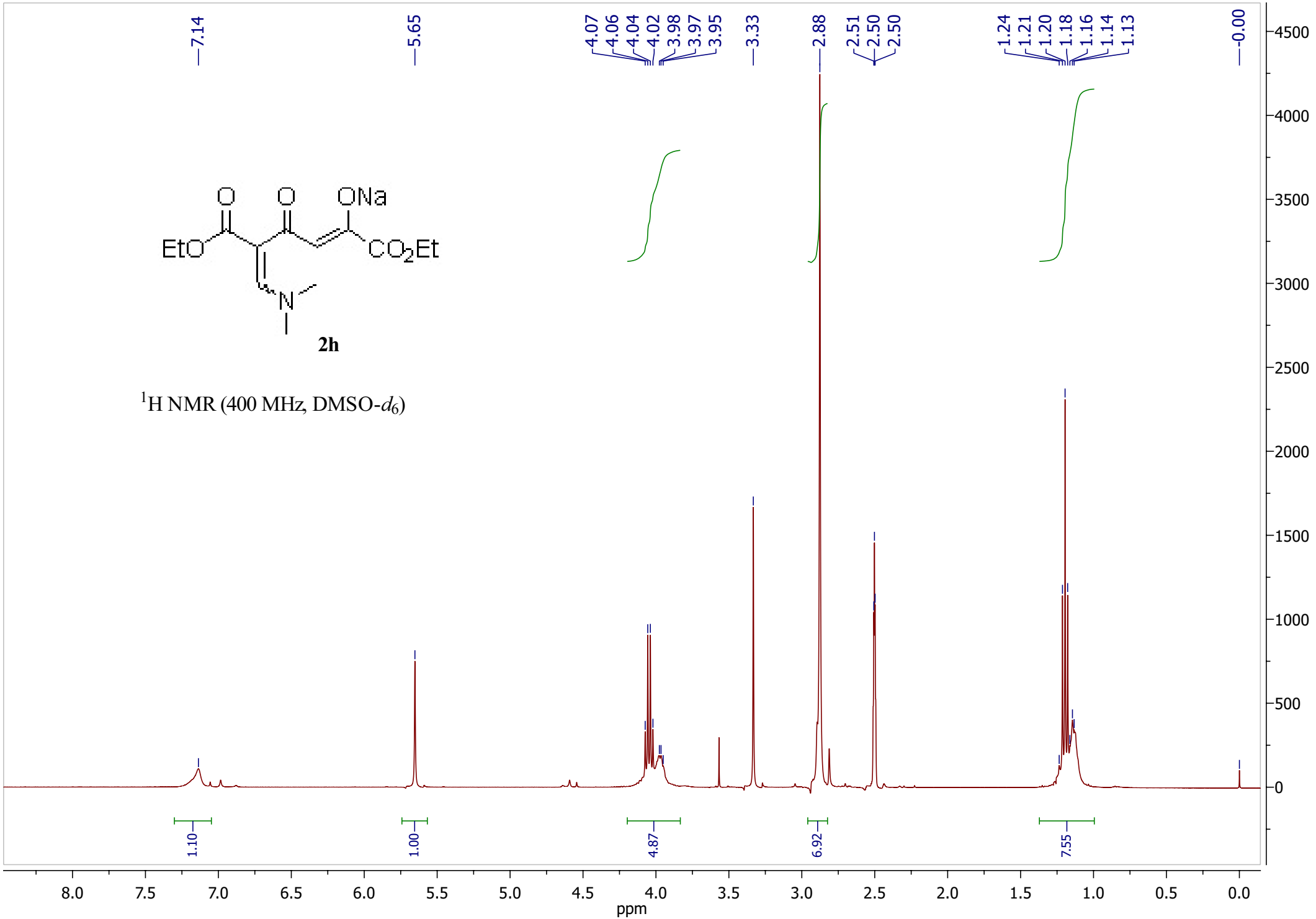

**2g**

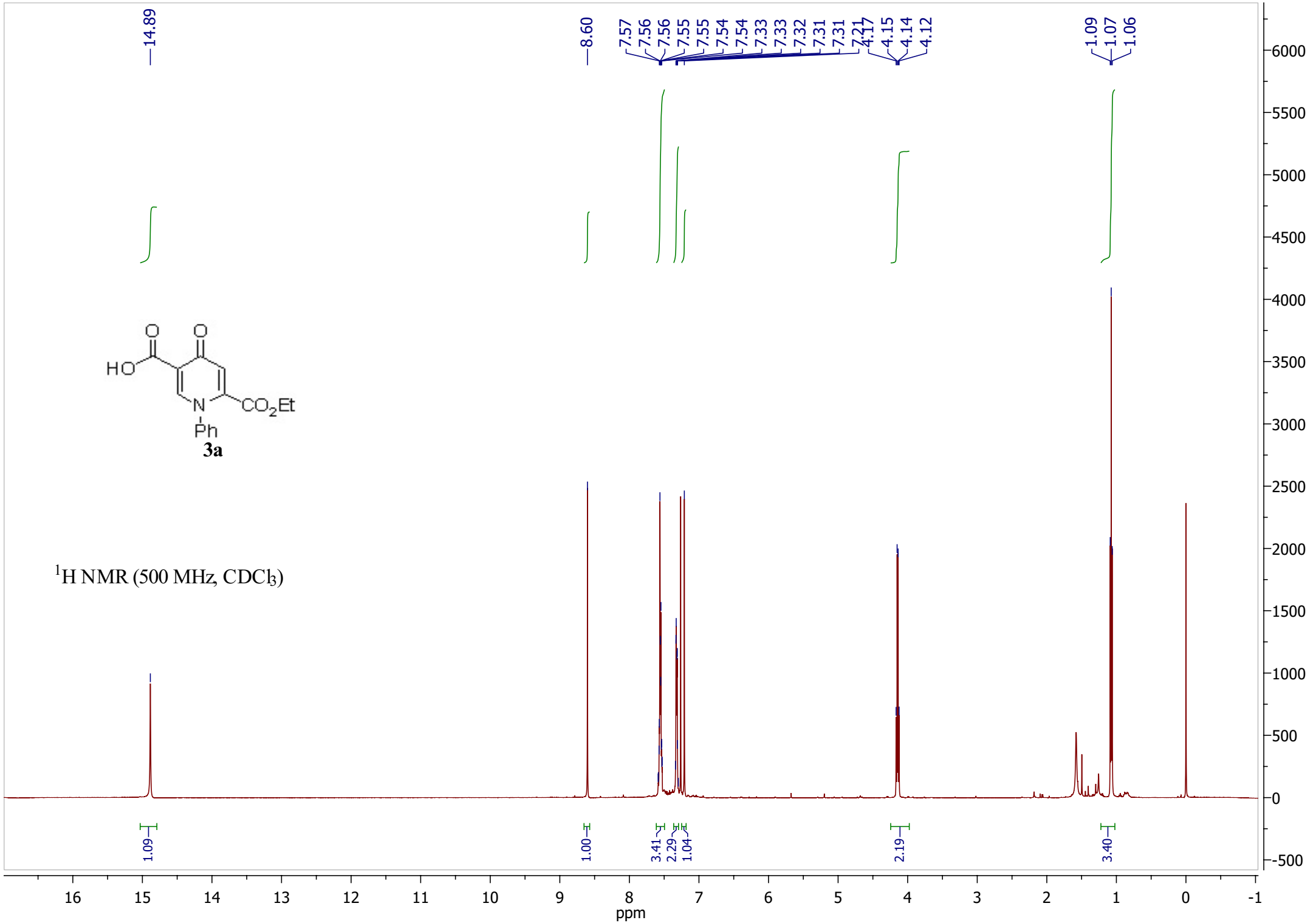
$^{19}$F NMR (376 MHz, $CDCl_3$)

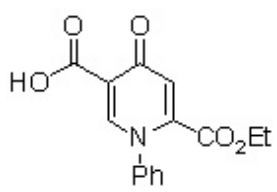



**2g**

$^{13}$C NMR (126 MHz, $CDCl_3$)

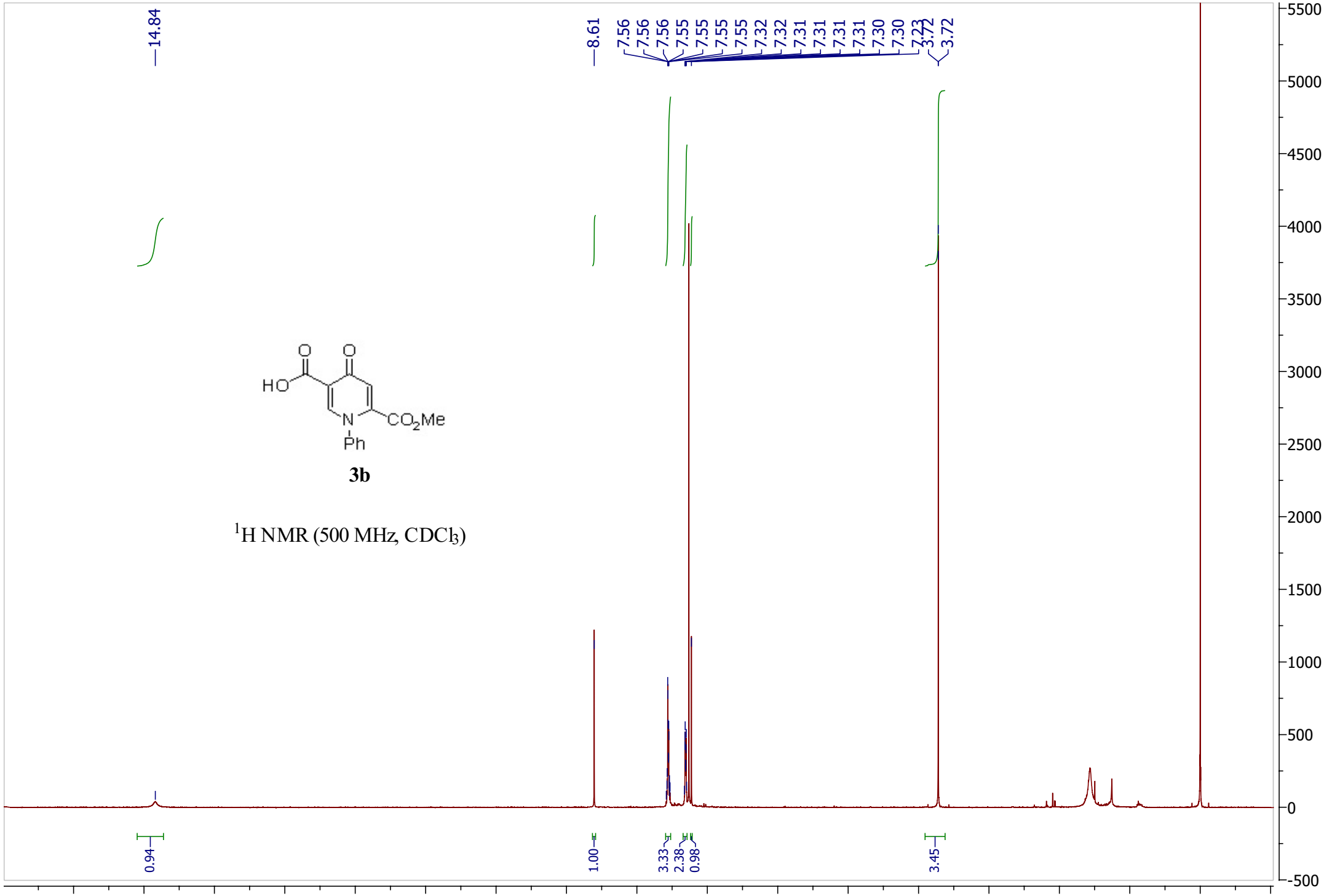

7.14
5.65
4.07
4.06
4.04
4.02
3.98
3.97
3.95
3.33
2.88
2.51
2.50
2.50
1.24
1.21
1.20
1.18
1.16
1.14
1.13
0.00
O
O
ONa
EtO
CO2Et
N
2h
1H NMR (400 MHz, DMSO-d6)
1.10
1.00
4.87
6.92
7.55
ppm


14.89
8.60
7.57
7.56
7.56
7.55
7.55
7.54
7.54
7.33
7.33
7.32
7.31
7.31
7.21
4.17
4.15
4.14
4.12
1.09
1.07
1.06
HO
O
O
N
Ph
CO2Et
3a
1H NMR (500 MHz, CDCl3)
1.09
1.00
3.41
2.29
1.04
2.19
3.40
ppm



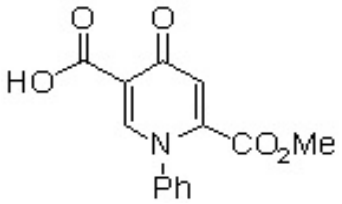

**3a**

$^{13}$C NMR (101 MHz, $CDCl_3$)



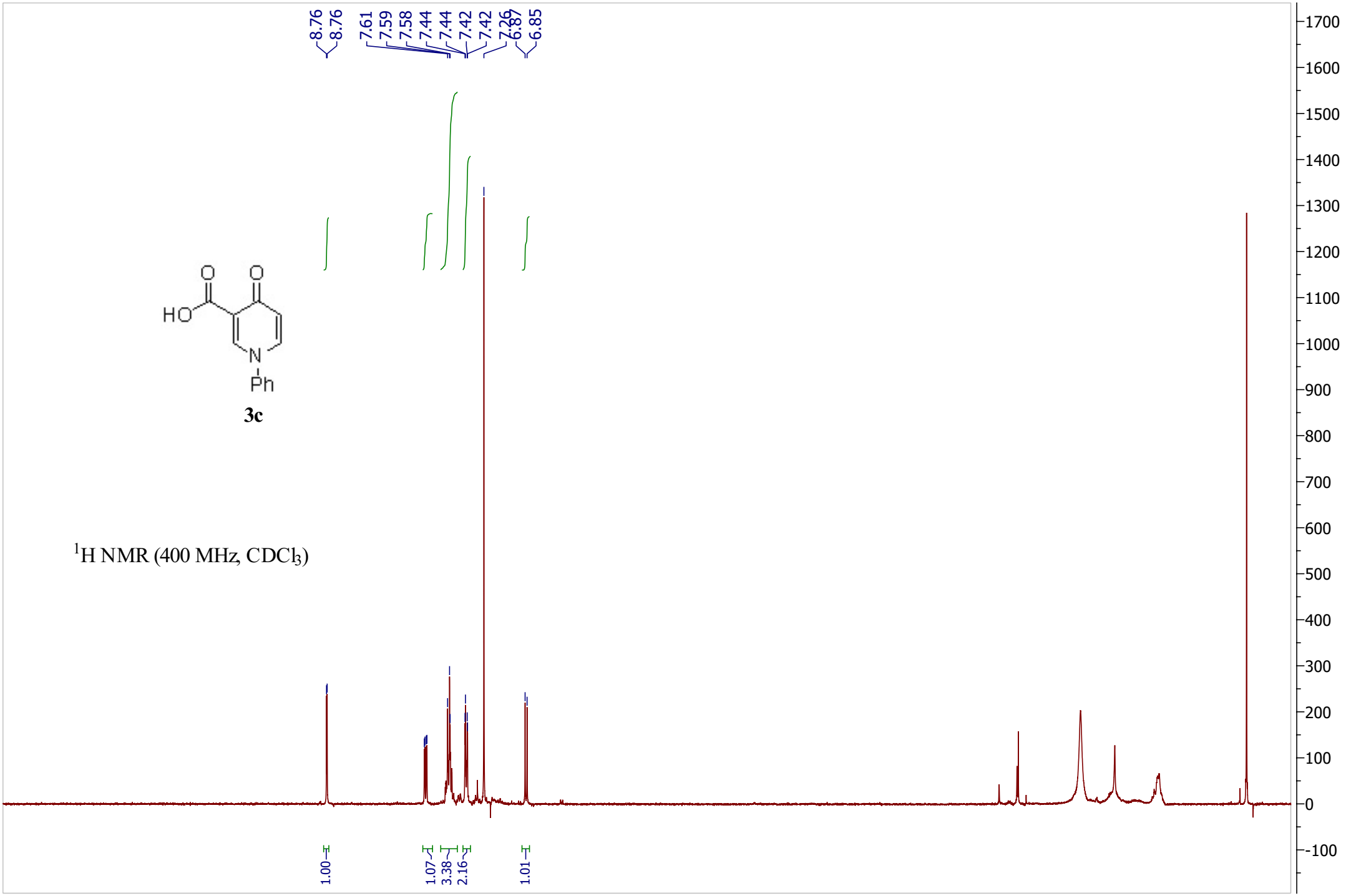

**3b**

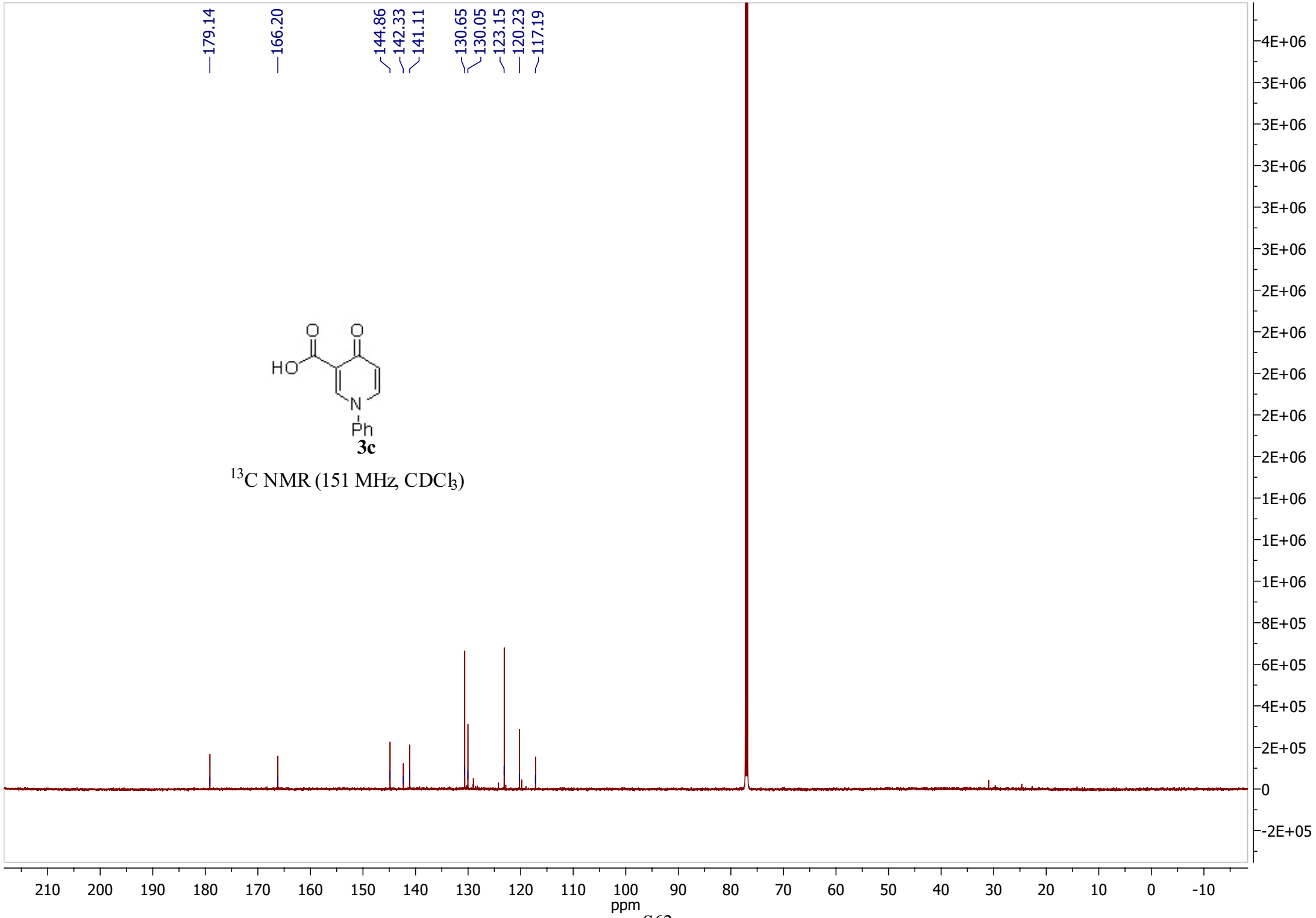
$^{1}$H NMR (500 MHz, $CDCl_3$)




**3b**

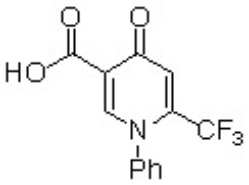
$^{13}$C NMR (101 MHz, $CDCl_3$)


8.76
8.76
7.61
7.59
7.58
7.44
7.44
7.42
7.42
7.26
6.87
6.85
HO
O
O
N
Ph
3c
$^1$H NMR (400 MHz, $CDCl_3$)
1.00
1.07
3.38
2.16
1.01
ppm



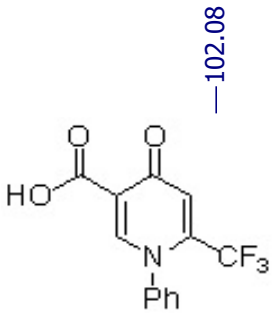

**3c**

$^{13}C$ NMR (151 MHz, $CDCl_3$)



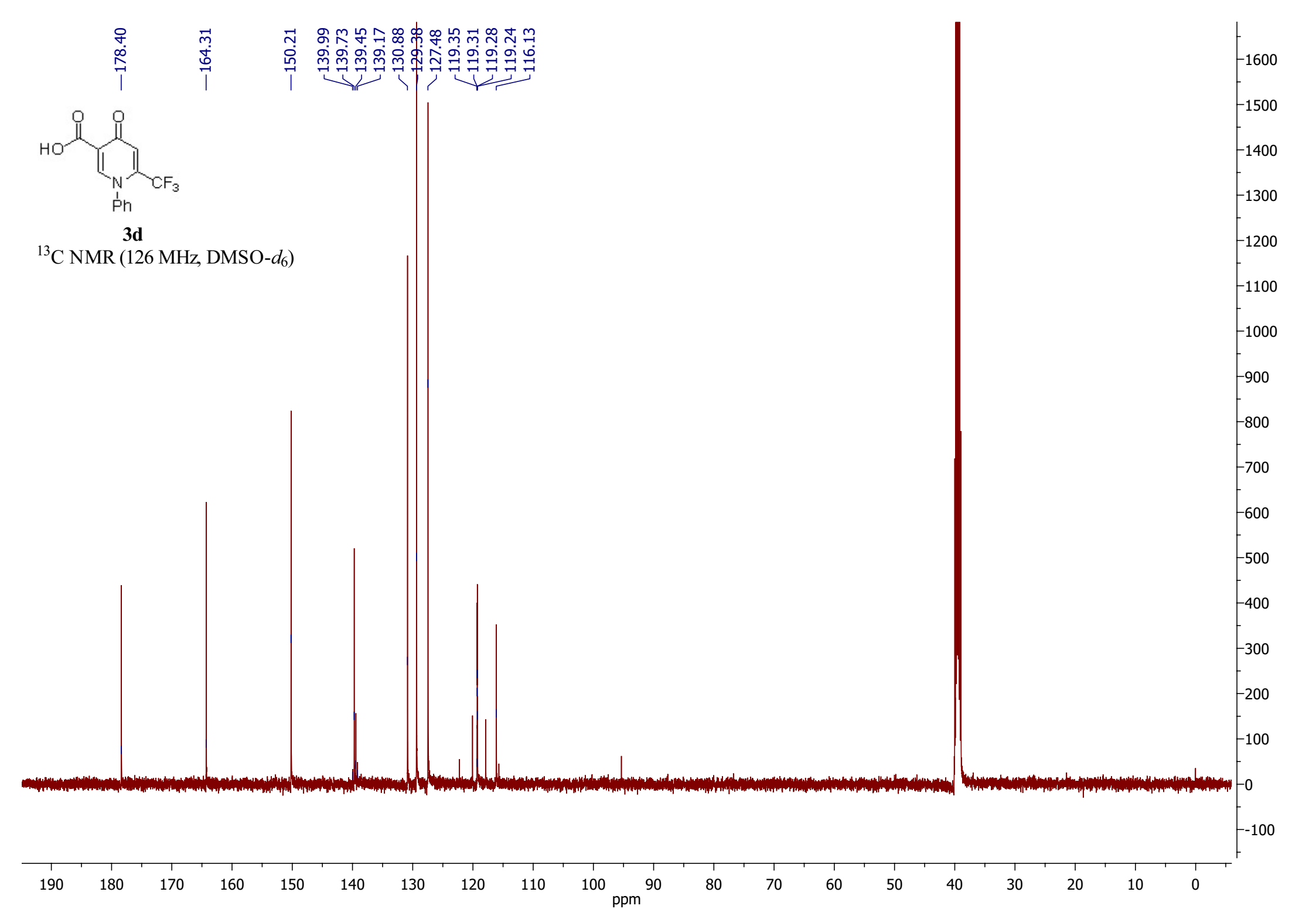

**3d**

$^1$H NMR (500 MHz, DMSO-$d_6$)



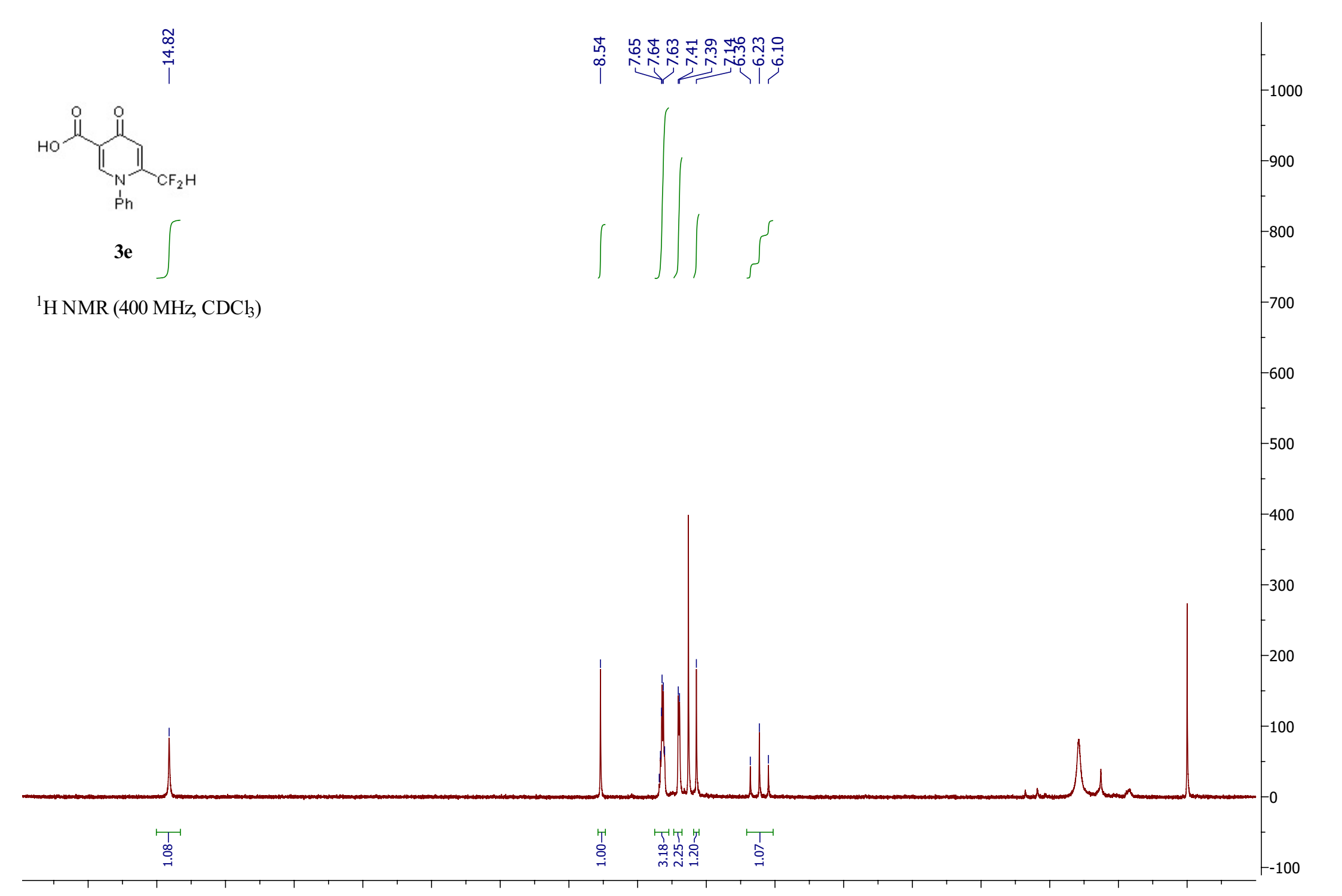

**3d**

$^{19}$F NMR (471 MHz, DMSO-$d_6$)

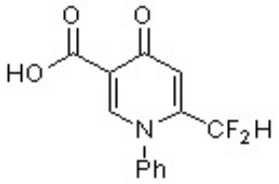



**3d**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



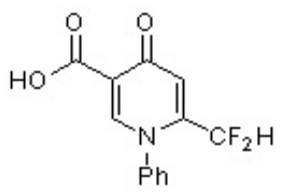

$^1$H NMR (400 MHz, $CDCl_3$)




45.04
44.90

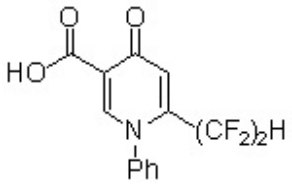
**3e**

$^{19}F$ NMR (376 MHz, $CDCl_3$)



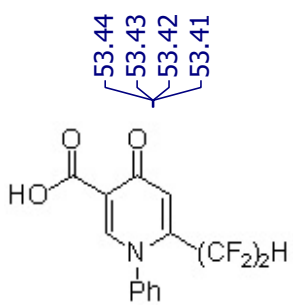

**3e**

$^{13}C$ NMR (101 MHz, $CDCl_3$)



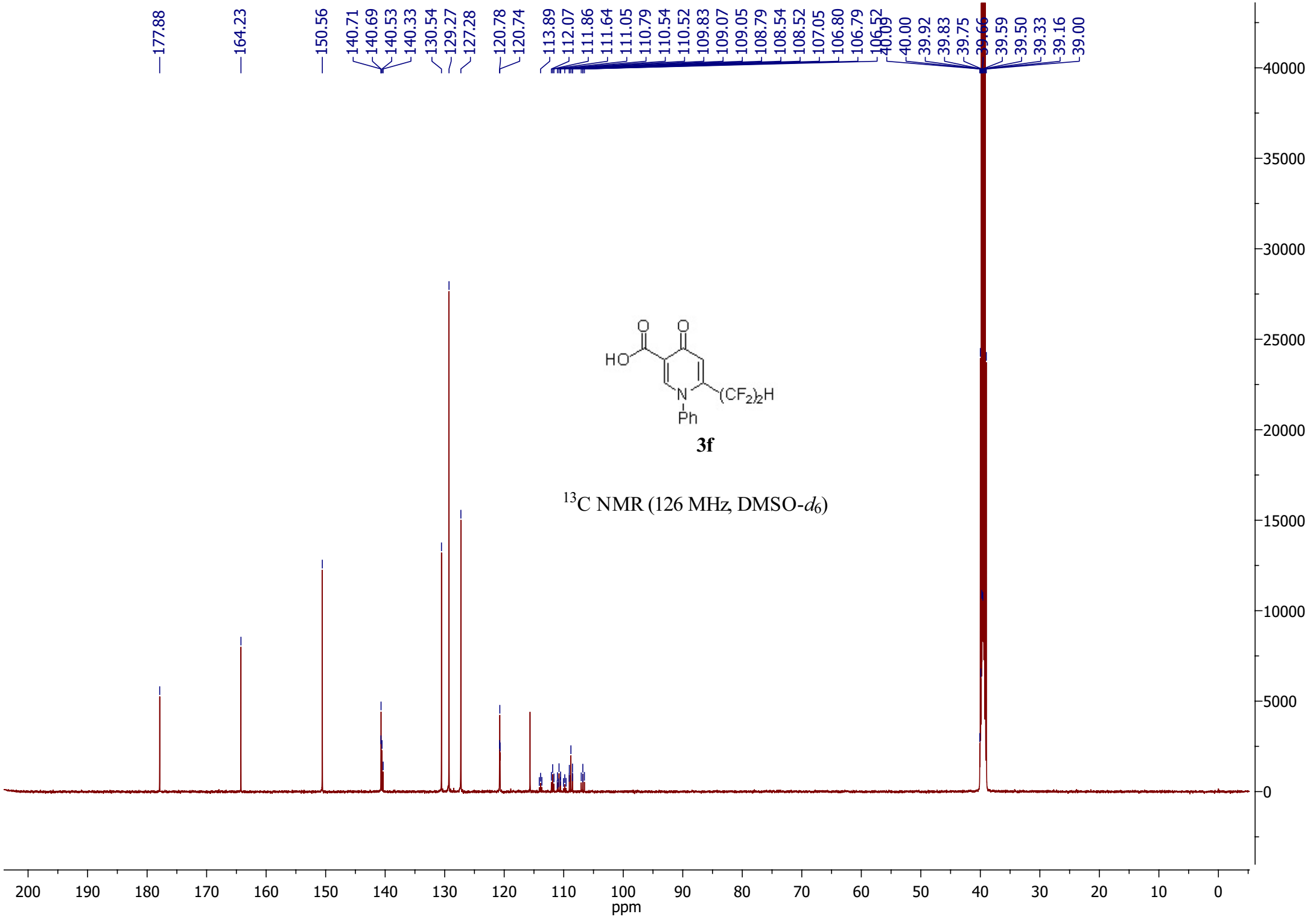

**3f**

$^1$H NMR (400 MHz, $CDCl_3$)



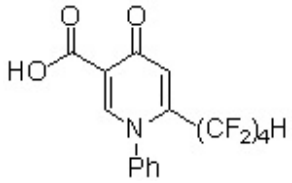

**3f**

$^{19}$F NMR (376 MHz, $CDCl_3$)



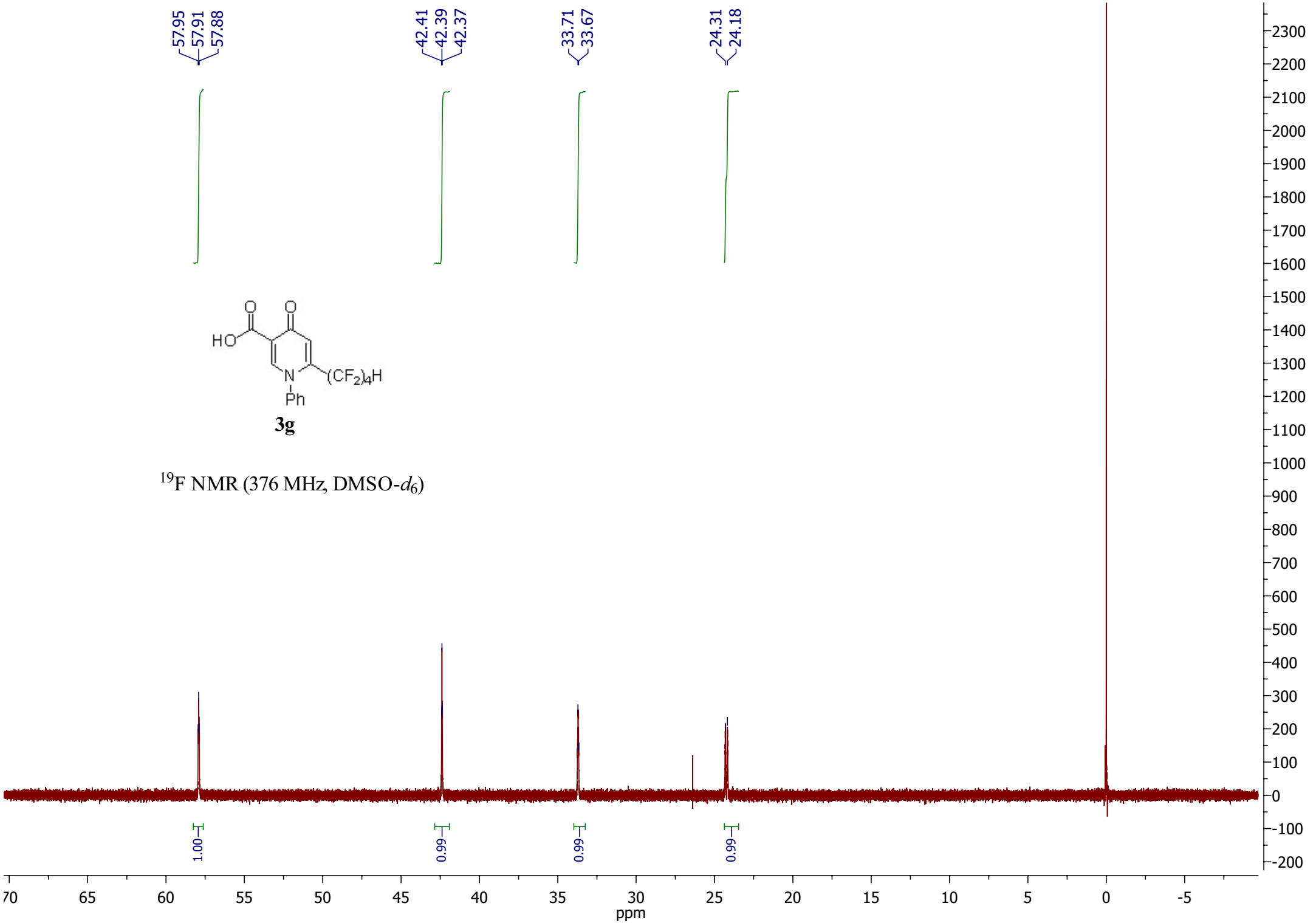

**3f**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



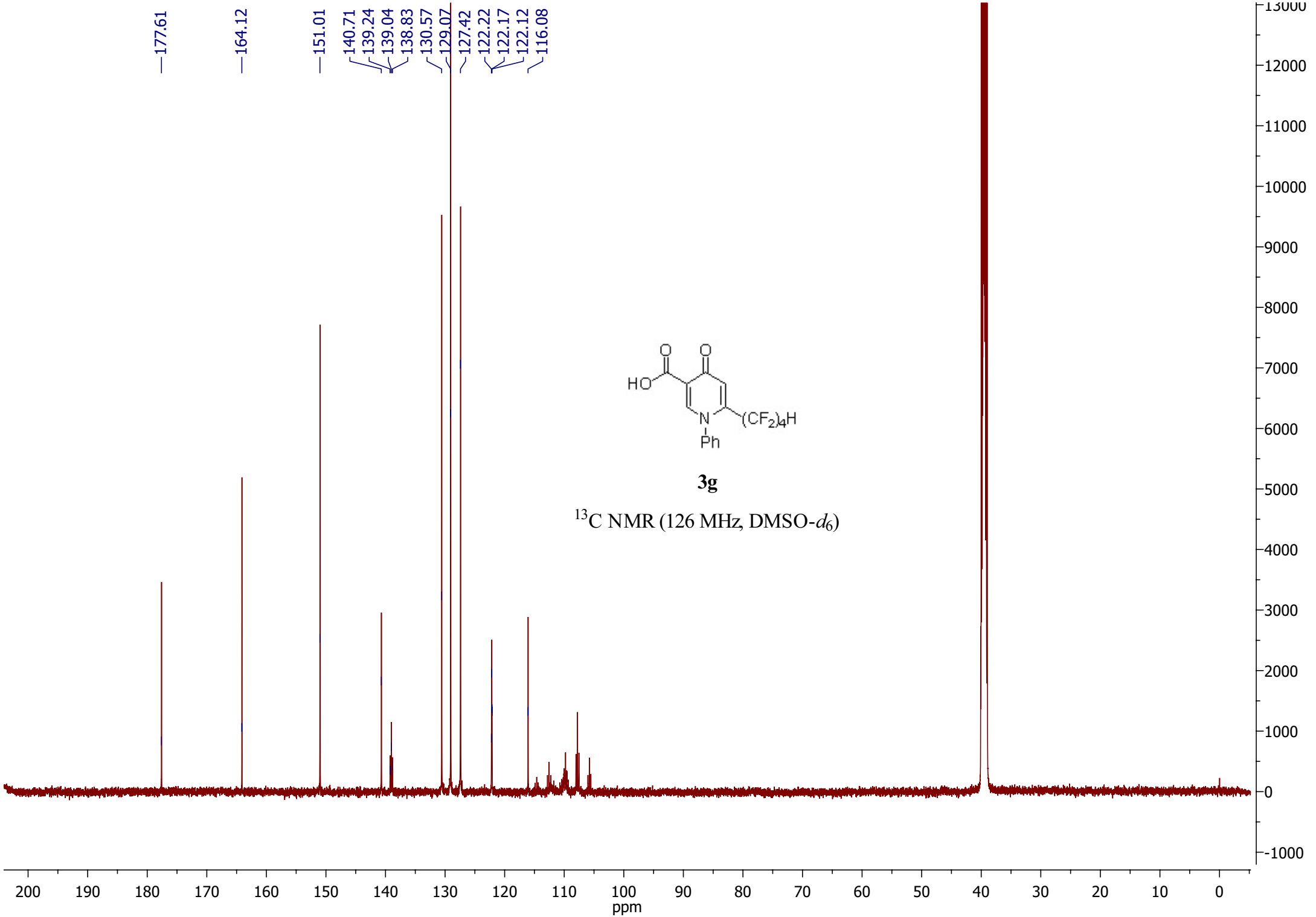

**3g**

$^1$H NMR (500 MHz, DMSO-$d_6$)



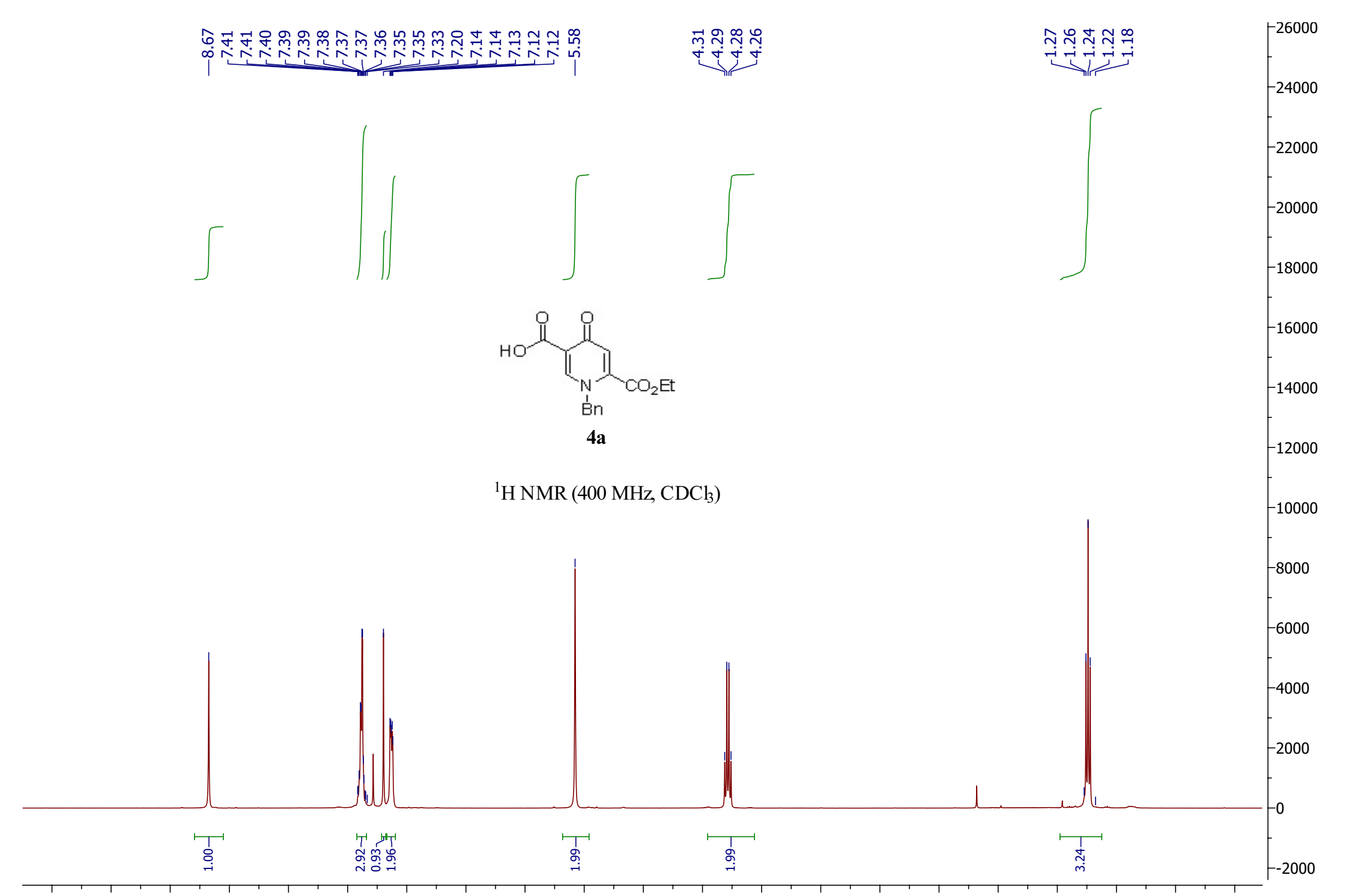

**3g**

$^{19}$F NMR (376 MHz, DMSO-$d_6$)



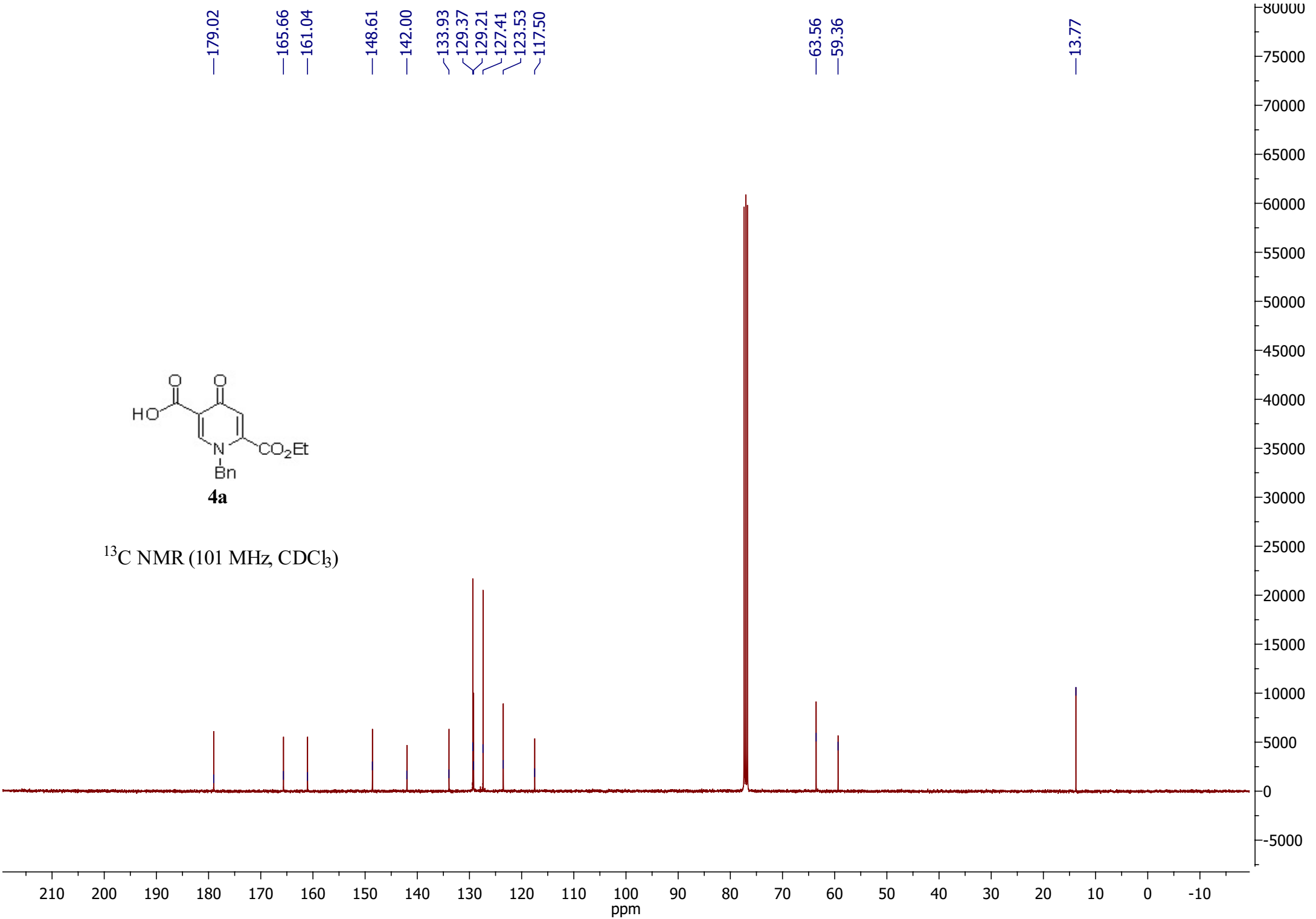

**3g**

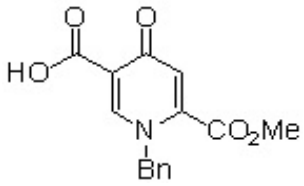
$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**4a**

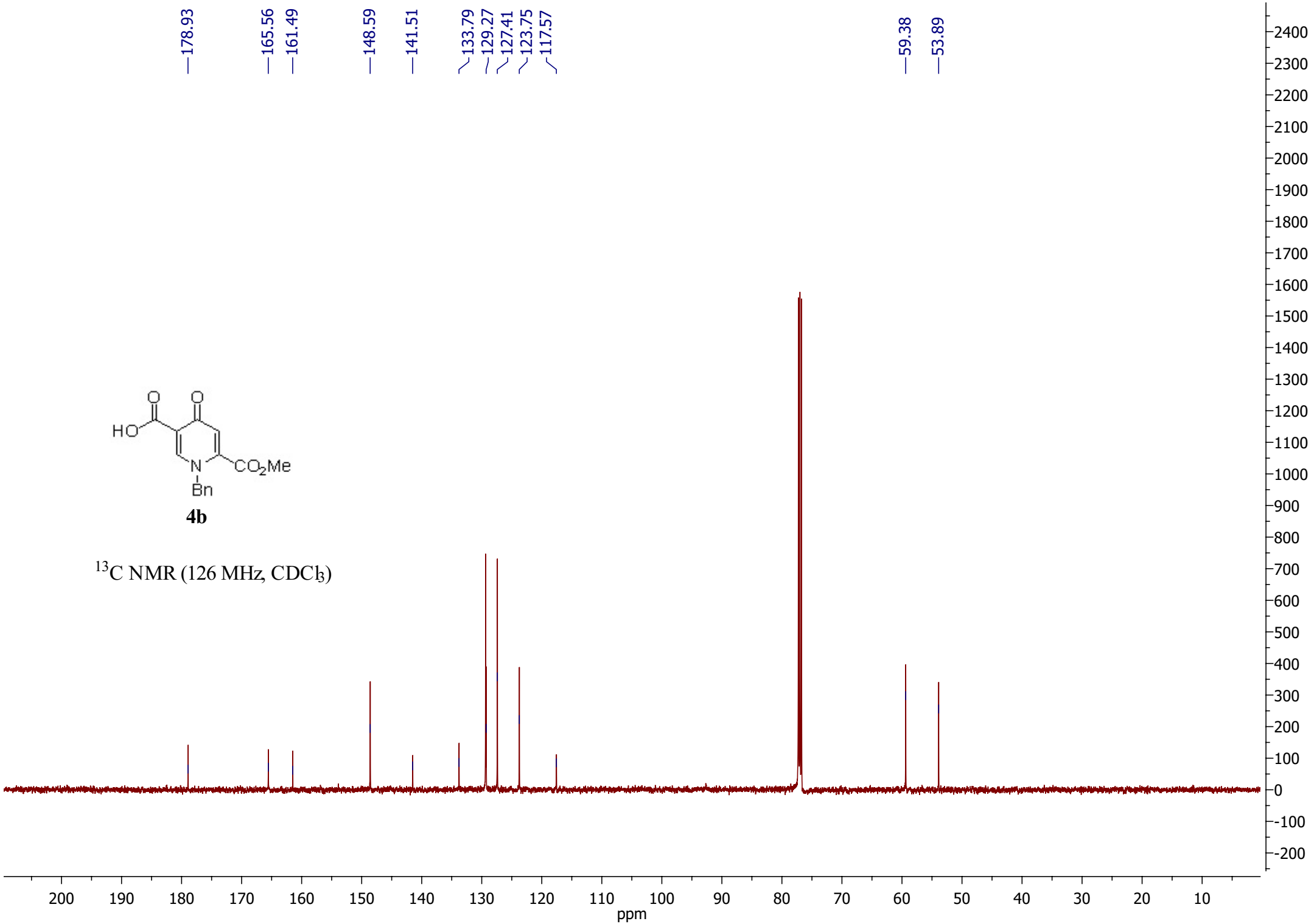
$^{1}$H NMR (400 MHz, $CDCl_3$)

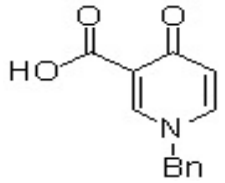

179.02
165.66
161.04
148.61
142.00
133.93
129.37
129.21
127.41
123.53
117.50
63.56
59.36
13.77
HO
O
O
N
Bn
CO2Et
4a
13C NMR (101 MHz, CDCl3)
ppm




**4b**

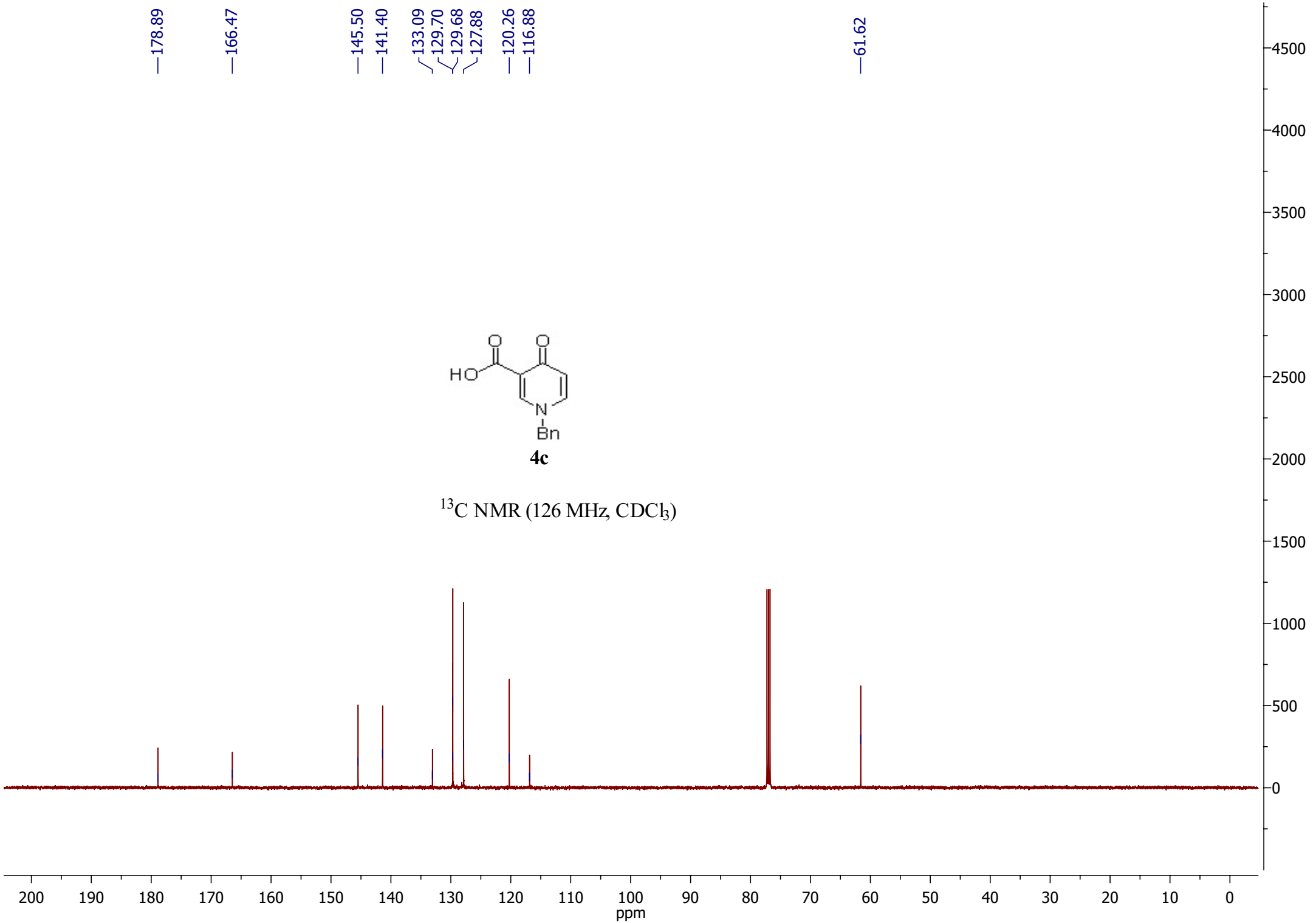
$^{1}$H NMR (400 MHz, $CDCl_3$)


178.93
165.56
161.49
148.59
141.51
133.79
129.27
127.41
123.75
117.57
59.38
53.89
HO
O
O
N
CO2Me
Bn
4b
13C NMR (126 MHz, CDCl3)
ppm



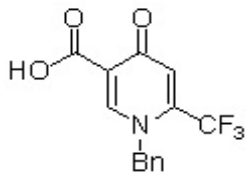

**4c**

$^1$H NMR (500 MHz, $CDCl_3$)



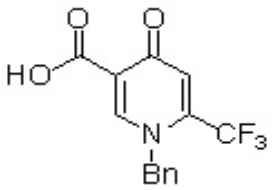

**4c**

$^{13}C$ NMR (126 MHz, $CDCl_3$)



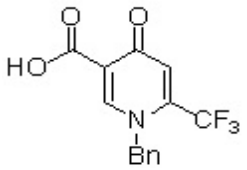

**4d**

$^1$H NMR (400 MHz, CDCl$_3$)



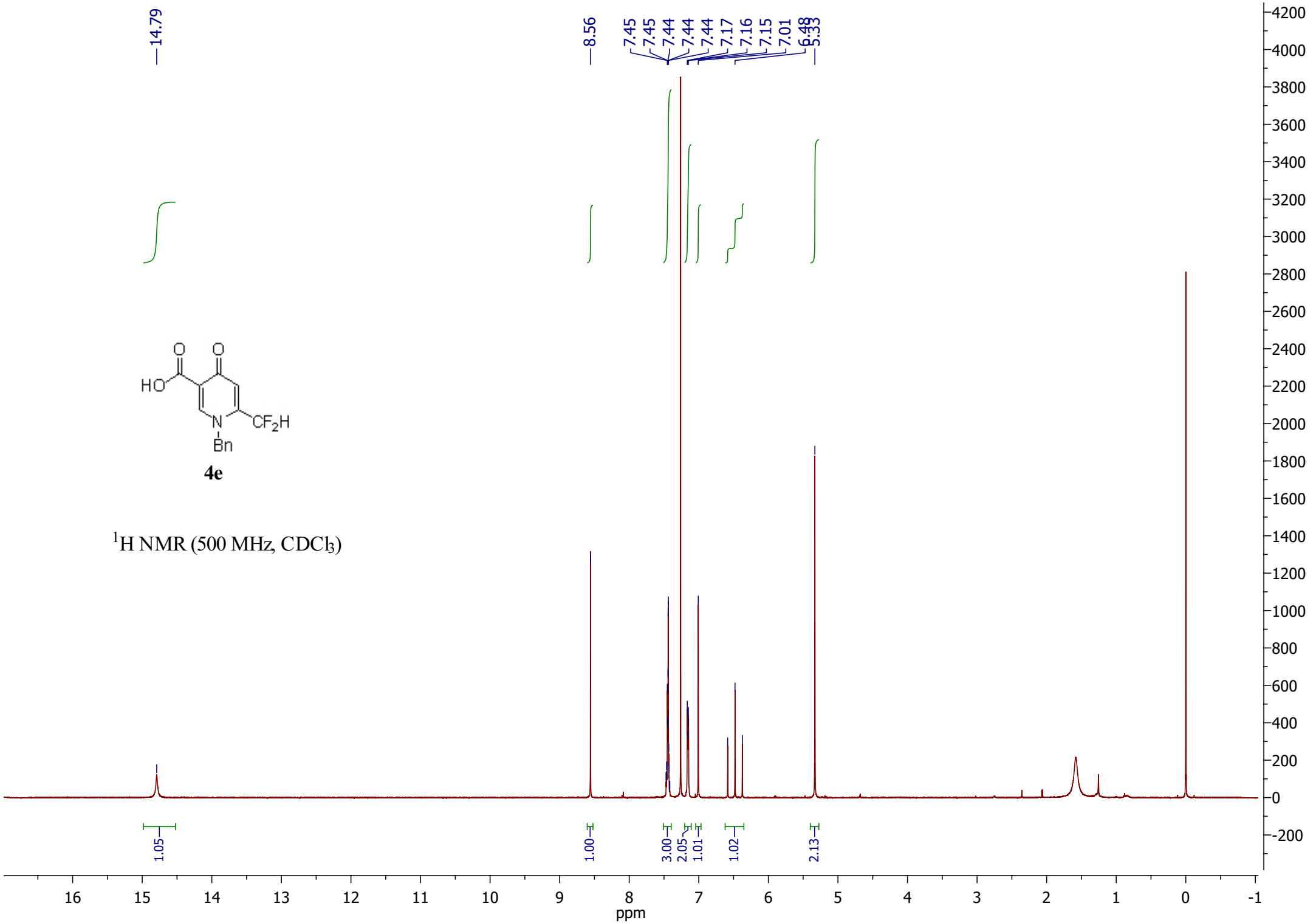
**4d**

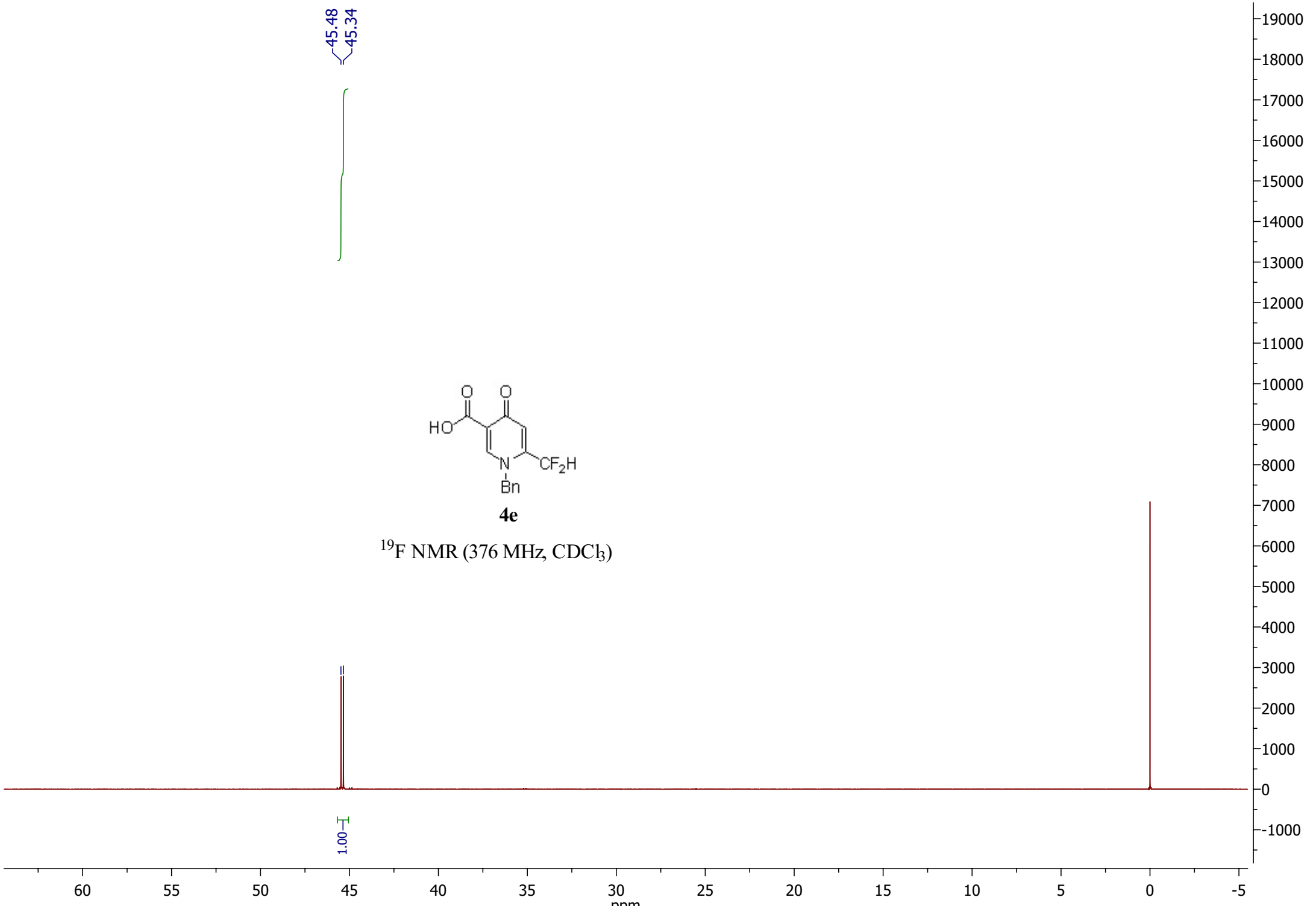
$^{19}F$ NMR (376 MHz, $CDCl_3$)



**4d**

$^{13}C$ NMR (151 MHz, $CDCl_3$)

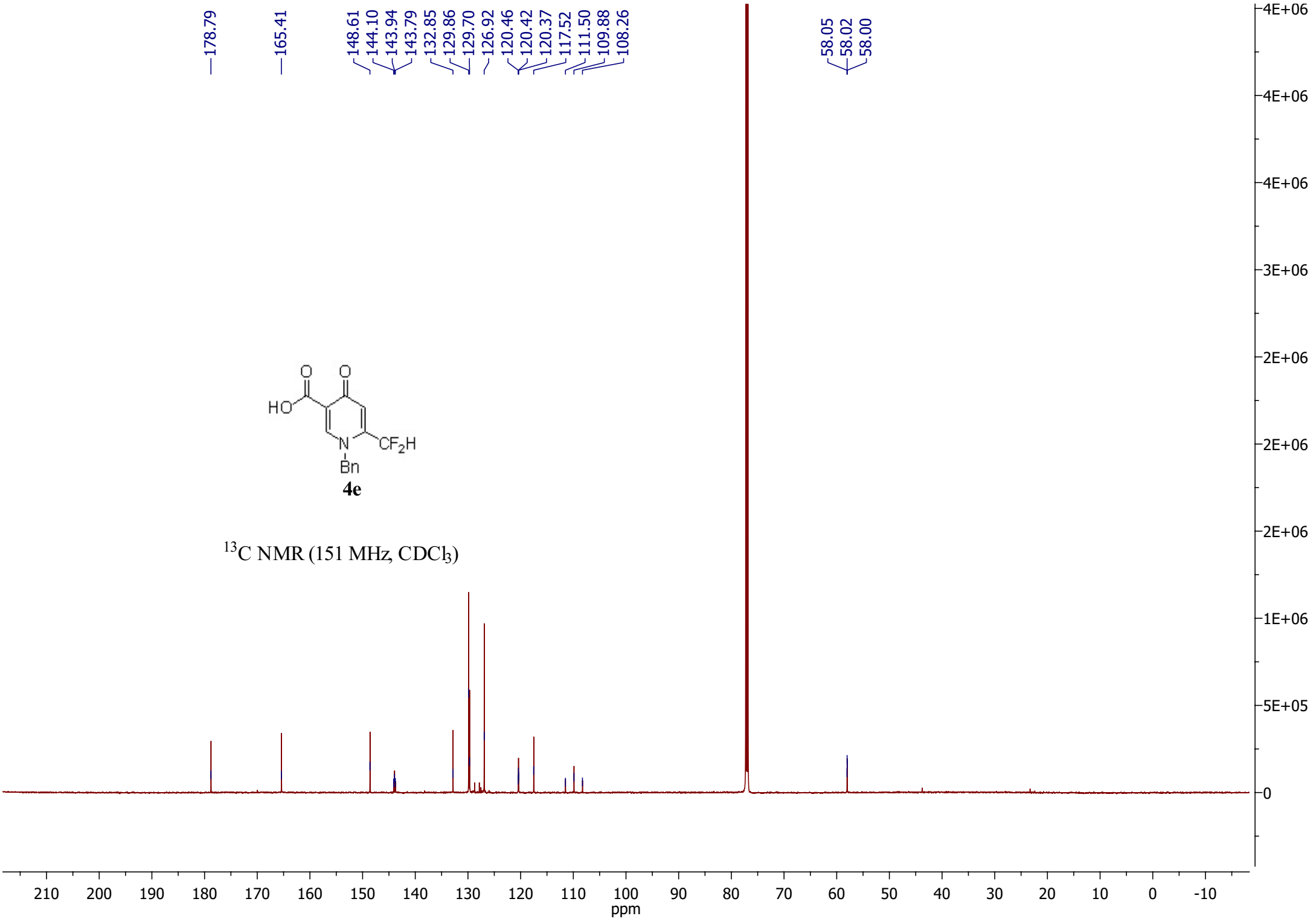

14.79
8.56
7.45
7.45
7.44
7.44
7.44
7.17
7.16
7.15
7.01
6.48
6.33
HO
O
O
N
Bn
CF2H
4e
1H NMR (500 MHz, CDCl3)
1.05
1.00
3.00
2.05
1.01
1.02
2.13
ppm





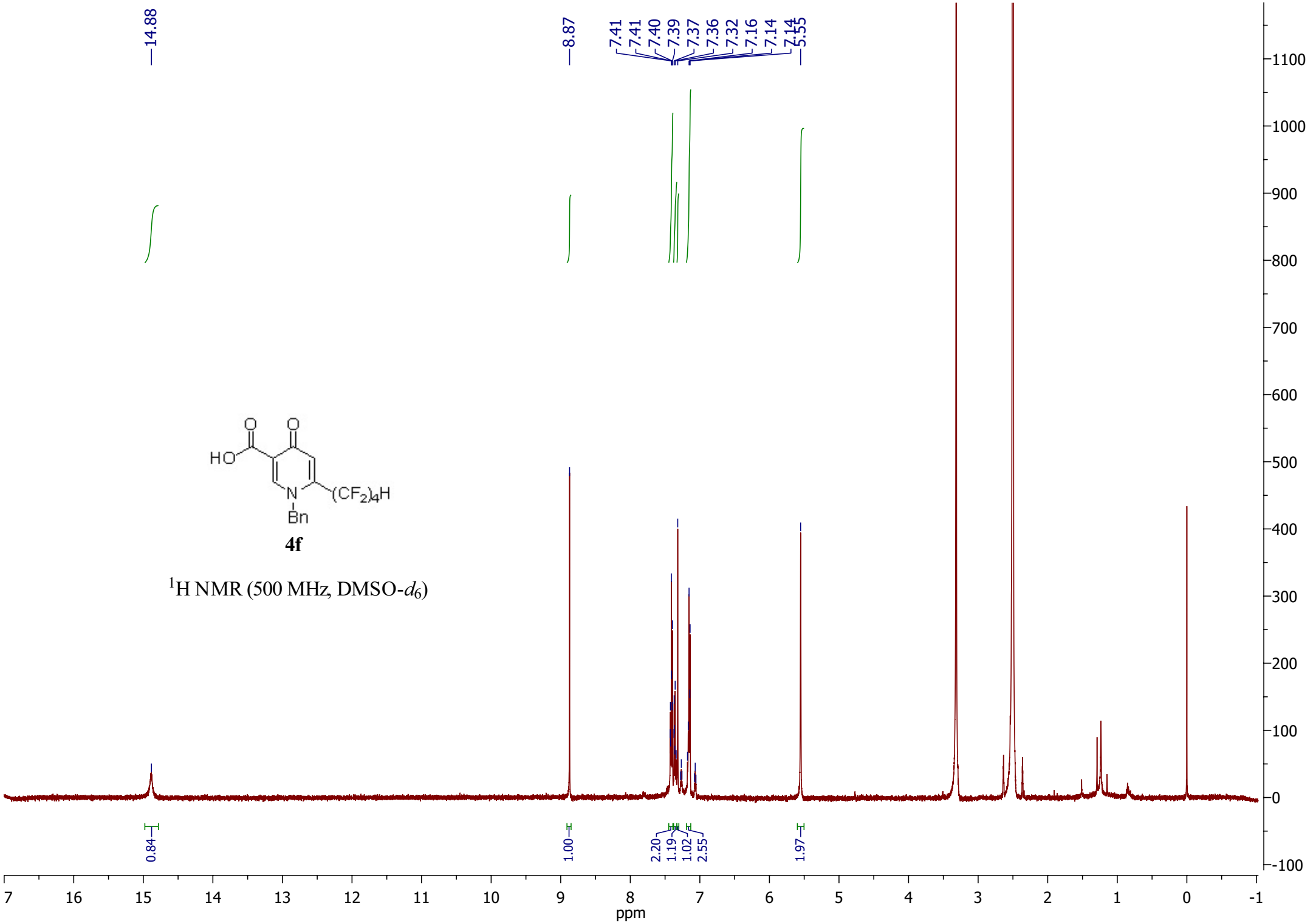

**4e**

$^{19}F$ NMR (376 MHz, $CDCl_3$)



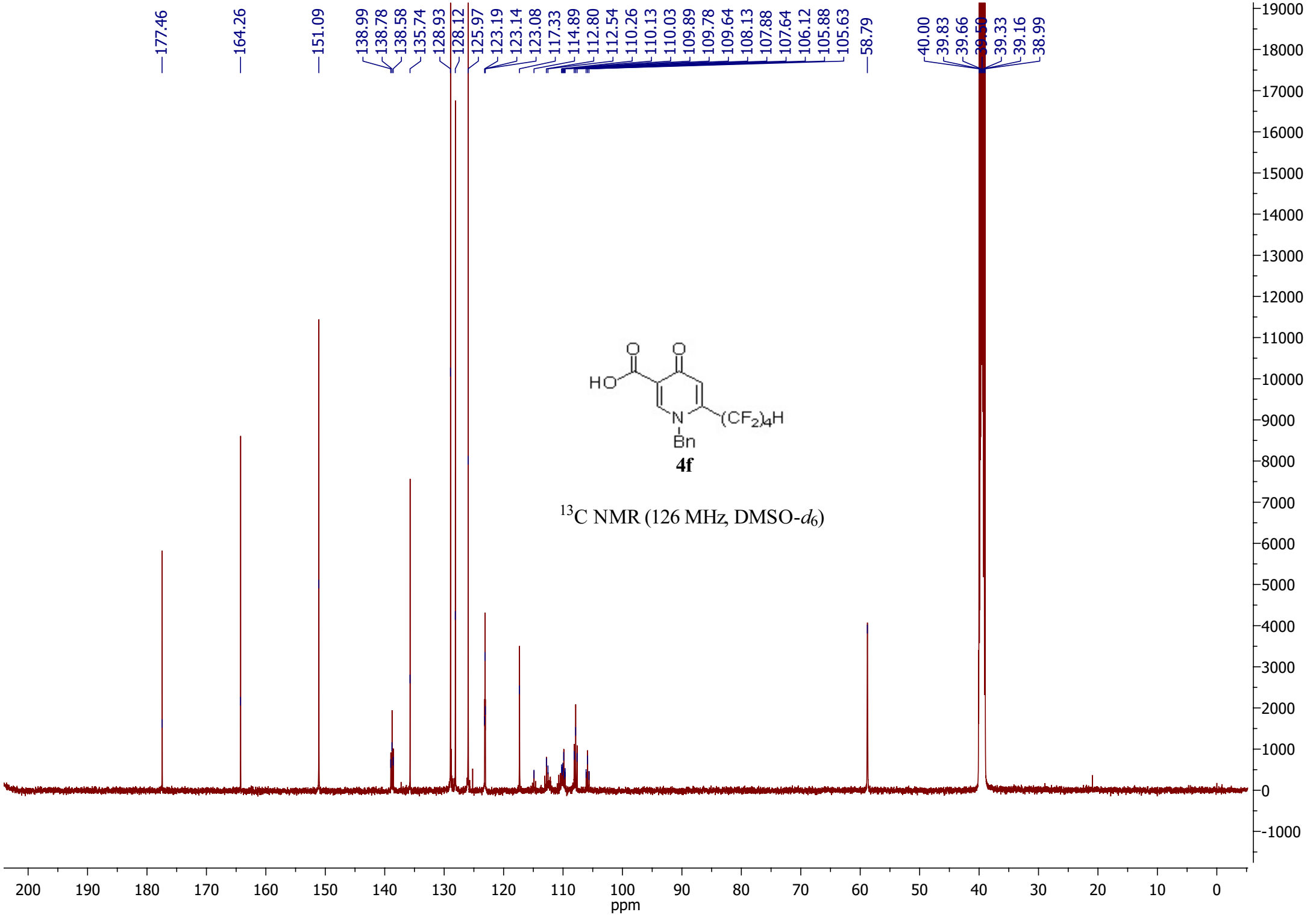

**4e**

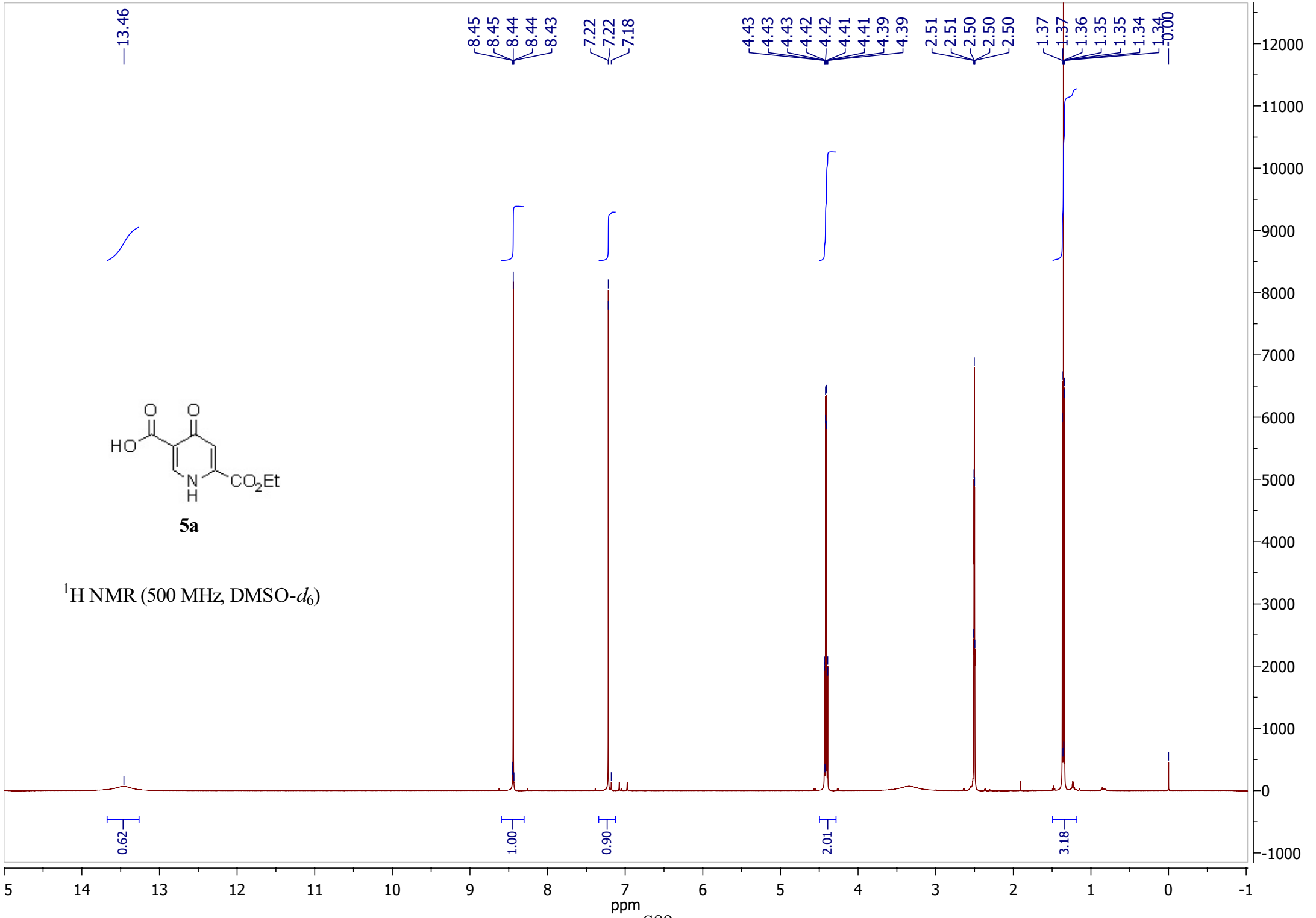
$^{13}$C NMR (151 MHz, $CDCl_3$)




**4f**

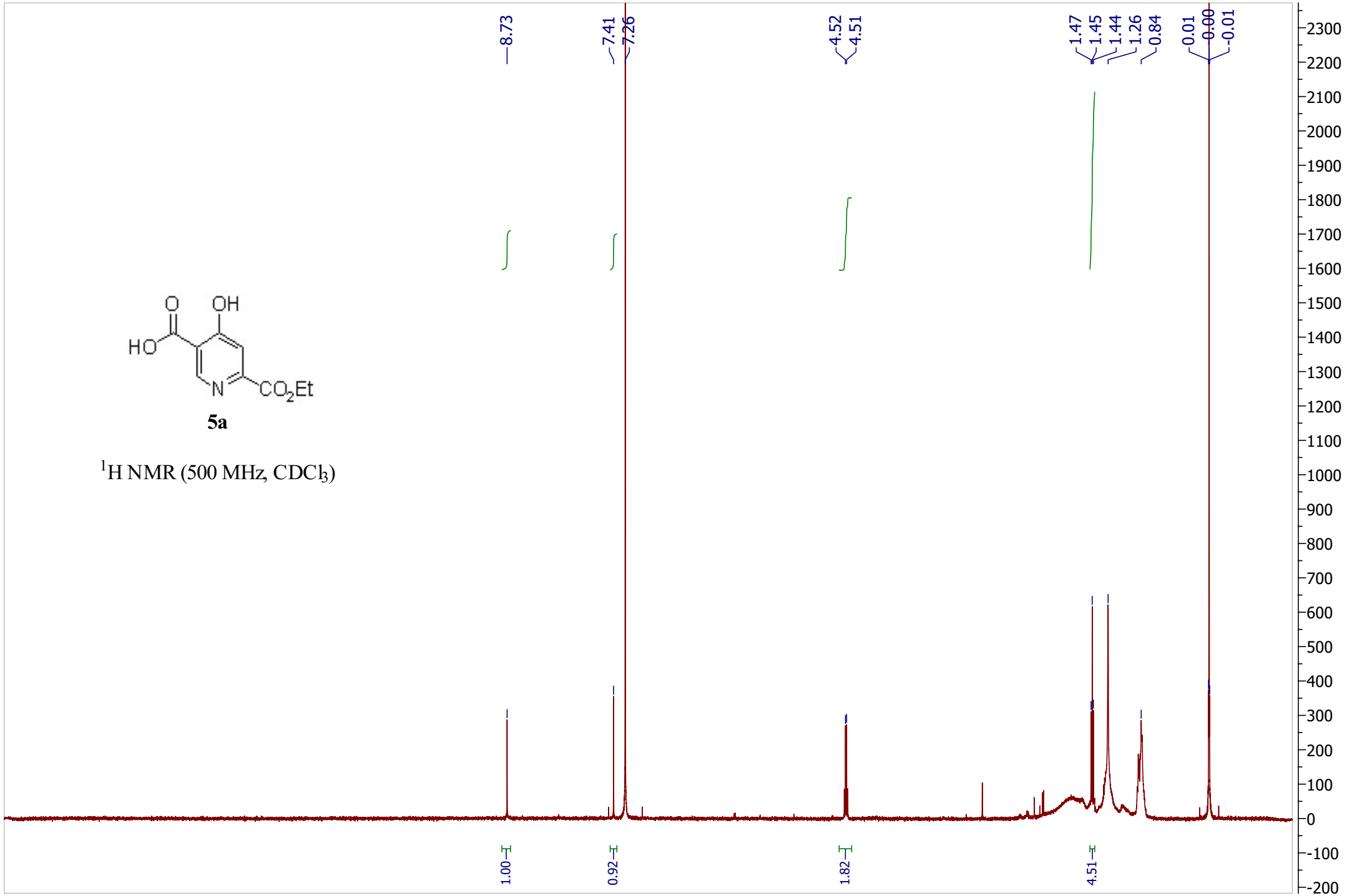
$^1$H NMR (500 MHz, DMSO-$d_6$)


177.46
164.26
151.09
138.99
138.78
138.58
135.74
128.93
128.12
125.97
123.19
123.14
123.08
117.33
114.89
112.80
112.54
110.26
110.13
110.03
109.89
109.78
109.64
108.13
107.88
107.64
106.12
105.88
105.63
58.79
40.00
39.83
39.66
39.50
39.33
39.16
38.99
HO
O
O
N
Bn
(CF2)4H
4f
13C NMR (126 MHz, DMSO-d6)
ppm



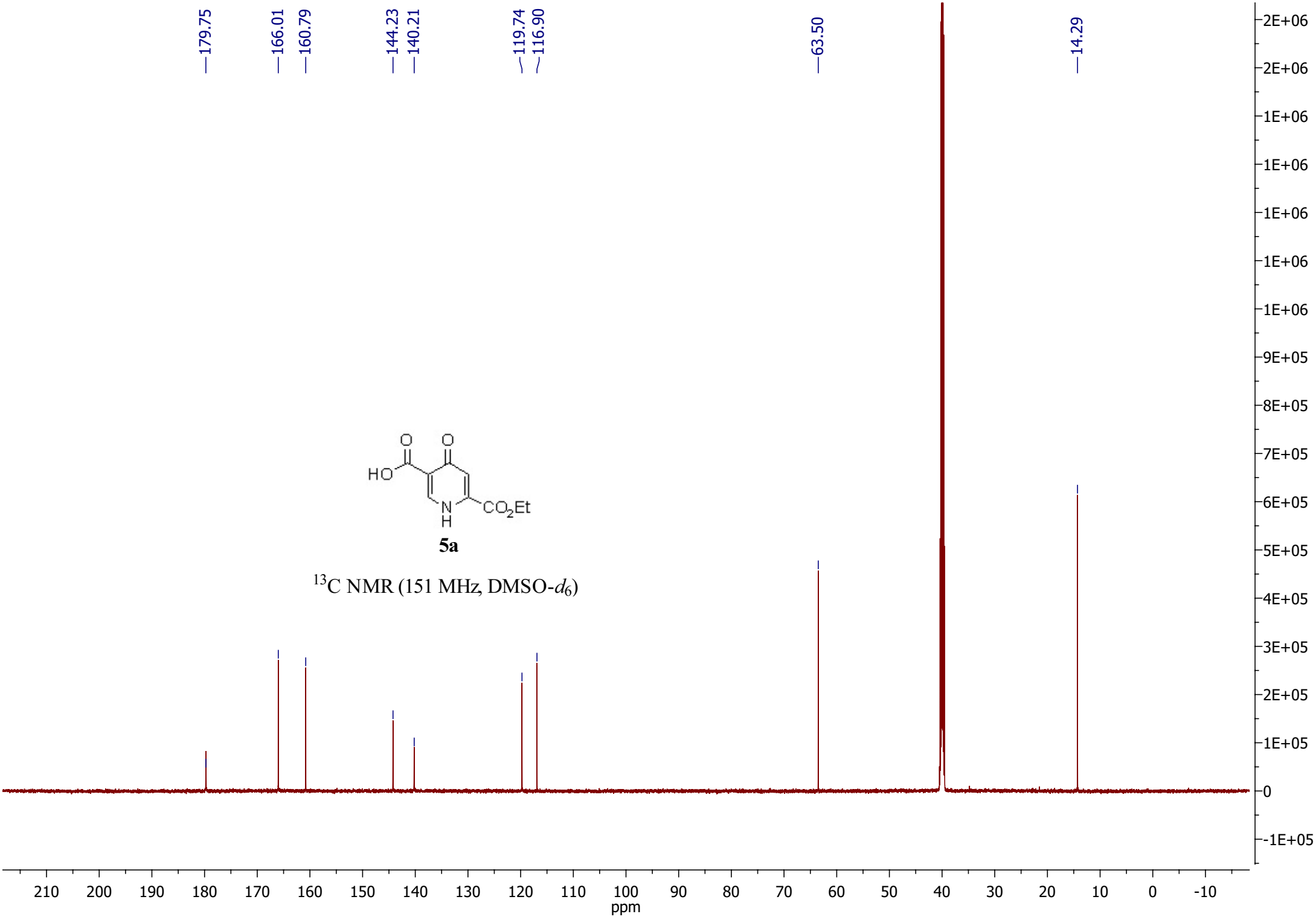

**5a**

$^1$H NMR (500 MHz, DMSO-$d_6$)



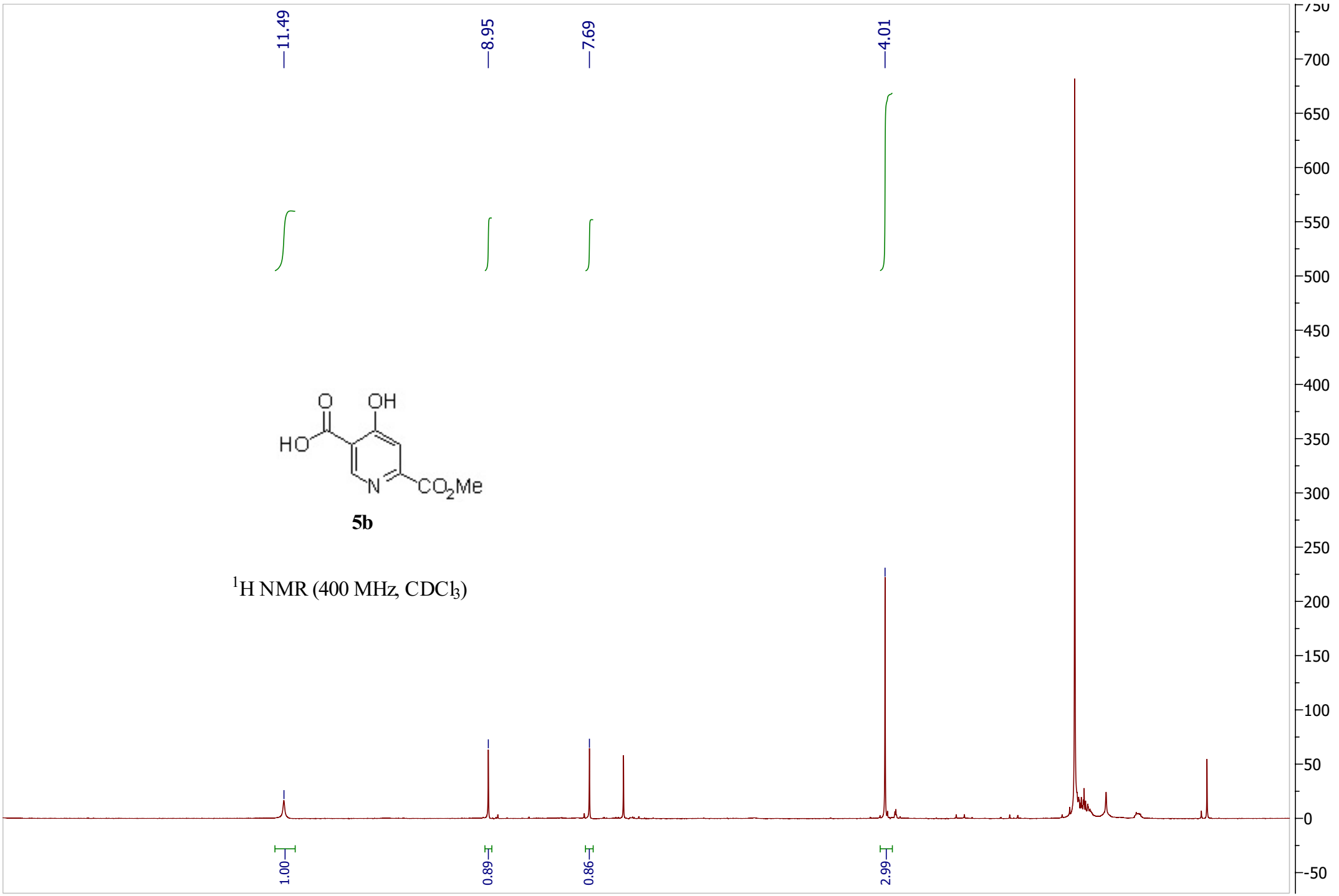

**5a**

$^1$H NMR (500 MHz, $CDCl_3$)



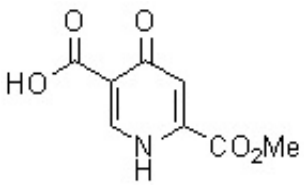

**5a**

$^{13}$C NMR (151 MHz, DMSO-$d_6$)



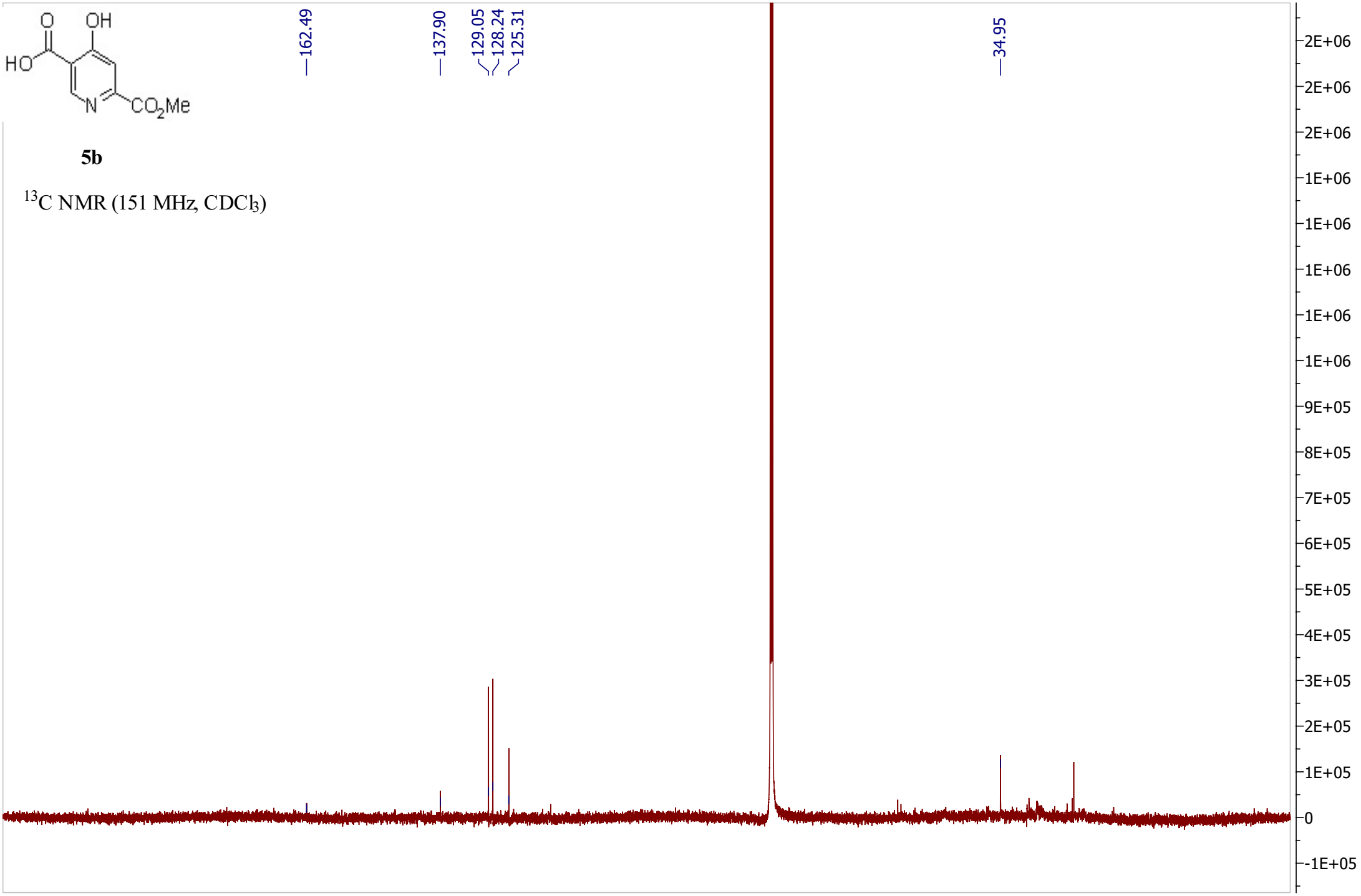

**5b**

$^1$H NMR (400 MHz, $CDCl_3$)



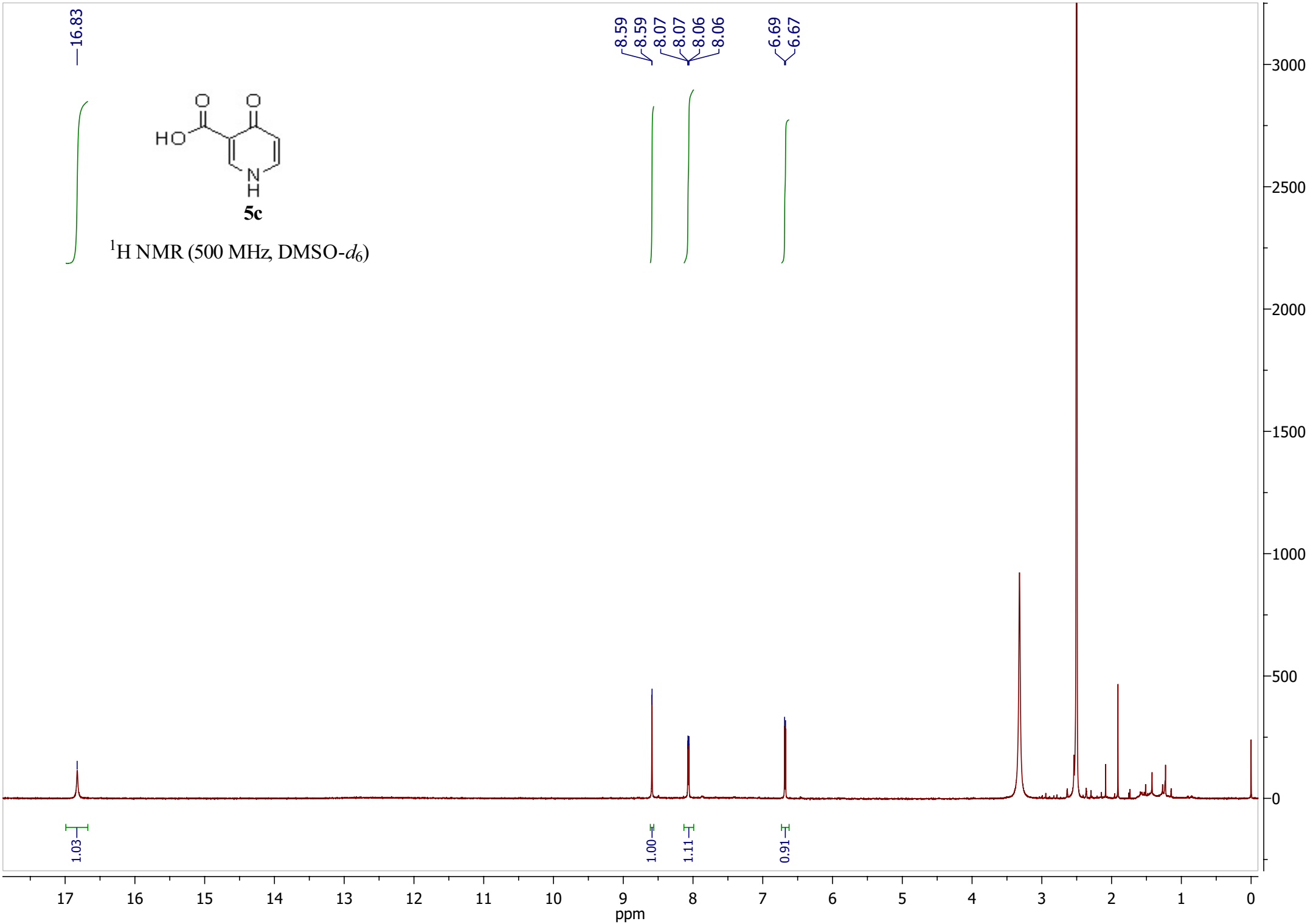

**5b**

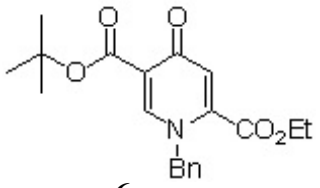
$^{1}$H NMR (500 MHz, DMSO-$d_6$)




**5b**

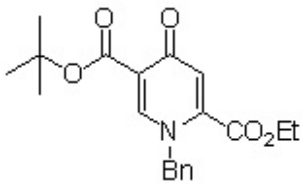
$^{13}C$ NMR (151 MHz, $CDCl_3$)


16.83
8.59
8.59
8.07
8.07
8.06
8.06
6.69
6.67
HO
O
O
N
H
5c
1H NMR (500 MHz, DMSO-d6)
1.03
1.00
1.11
0.91
3000
2500
2000
1500
1000
500
0
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm



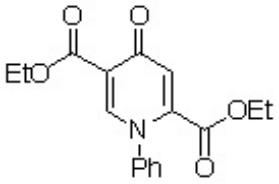
**6a**

$^1$H NMR (500 MHz, DMSO-$d_6$)



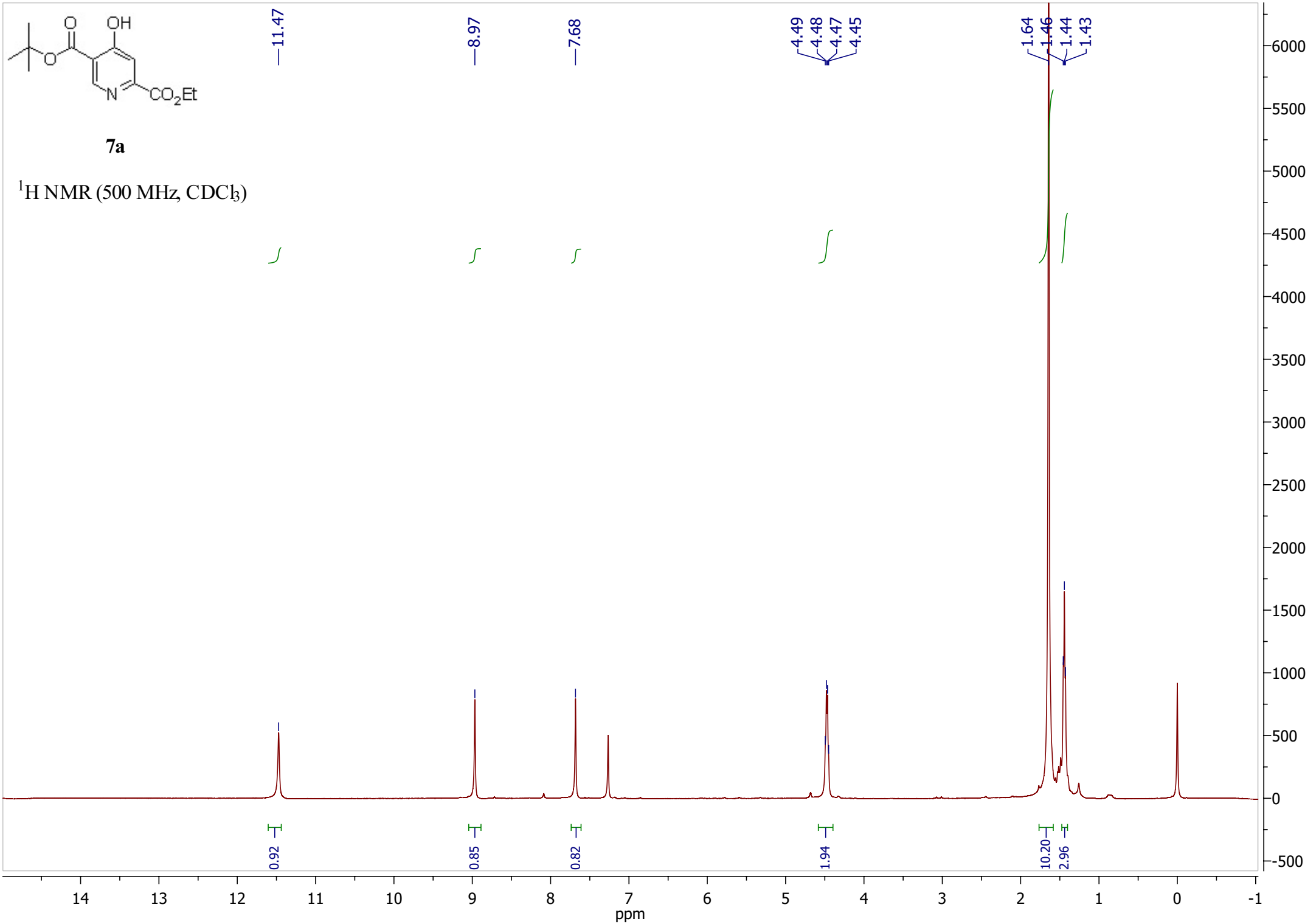

**6a**

$^{13}$C NMR (151 MHz, $CDCl_3$)



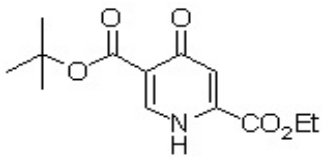

**6b**

$^1$H NMR (400 MHz, DMSO-$d_6$)



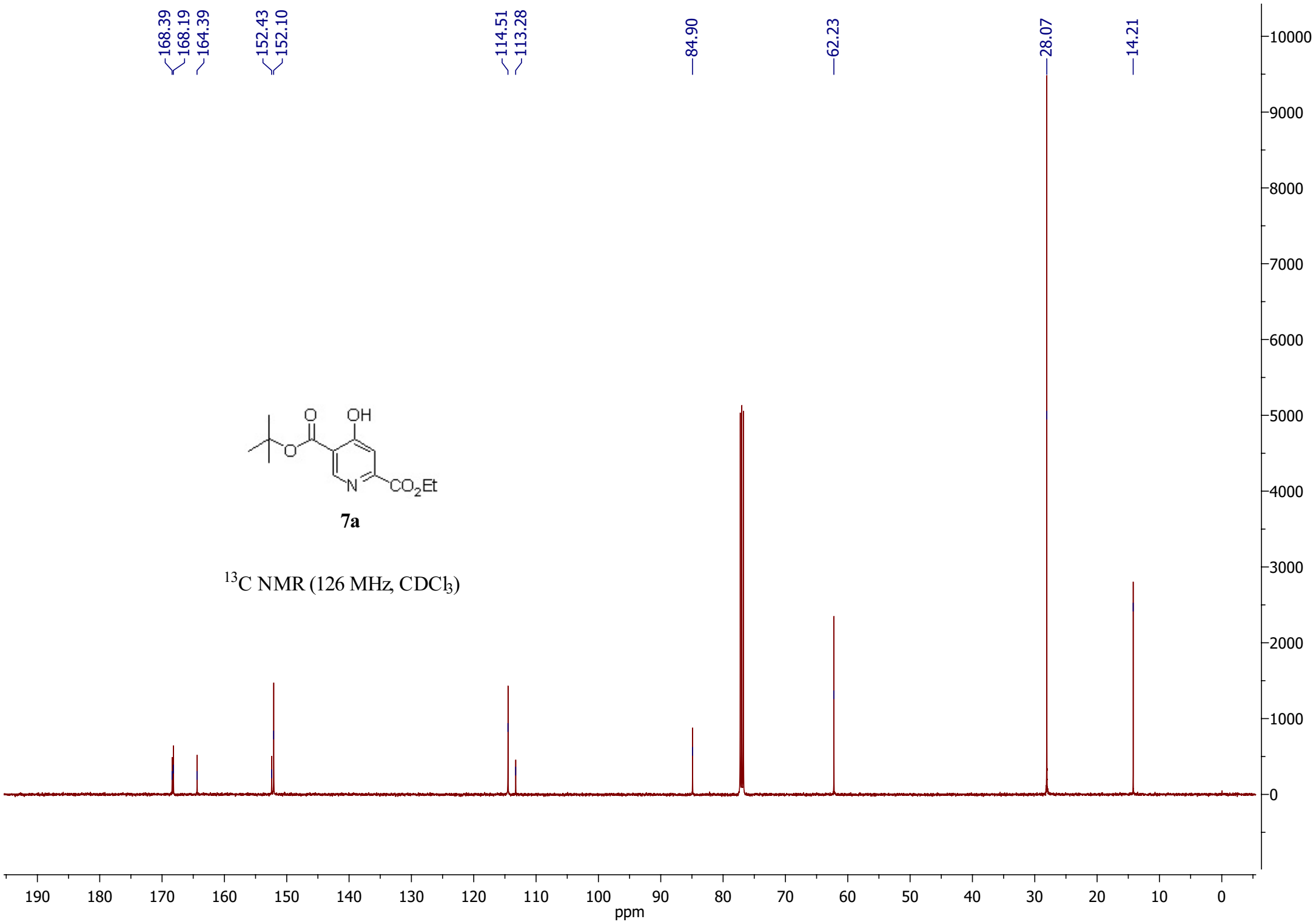

**7a**

$^1$H NMR (500 MHz, $CDCl_3$)



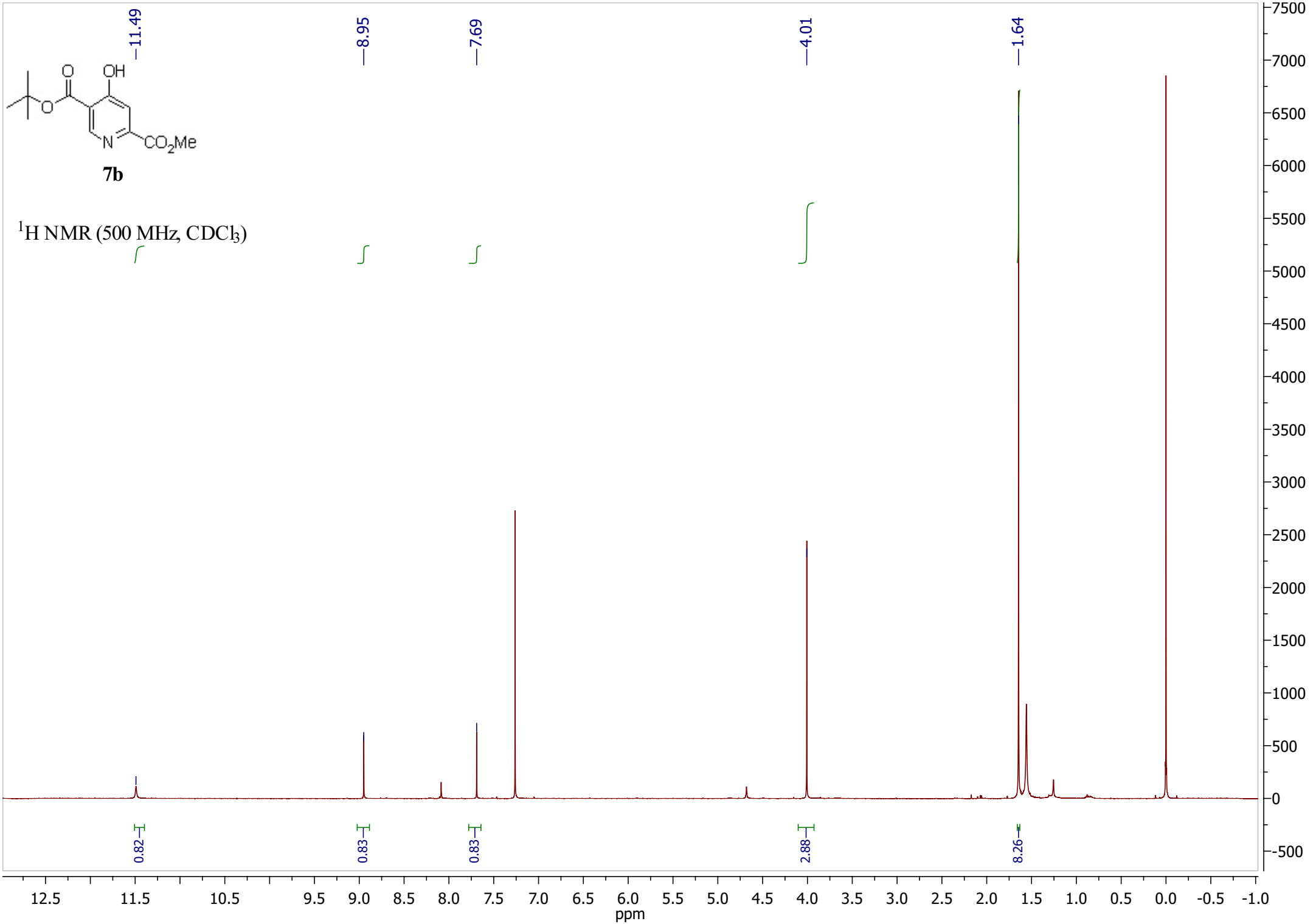
**7a**

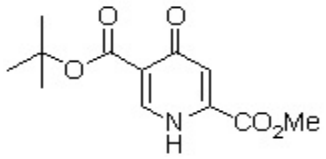
$^1$H NMR (500 MHz, DMSO-$d_6$)




**7a**

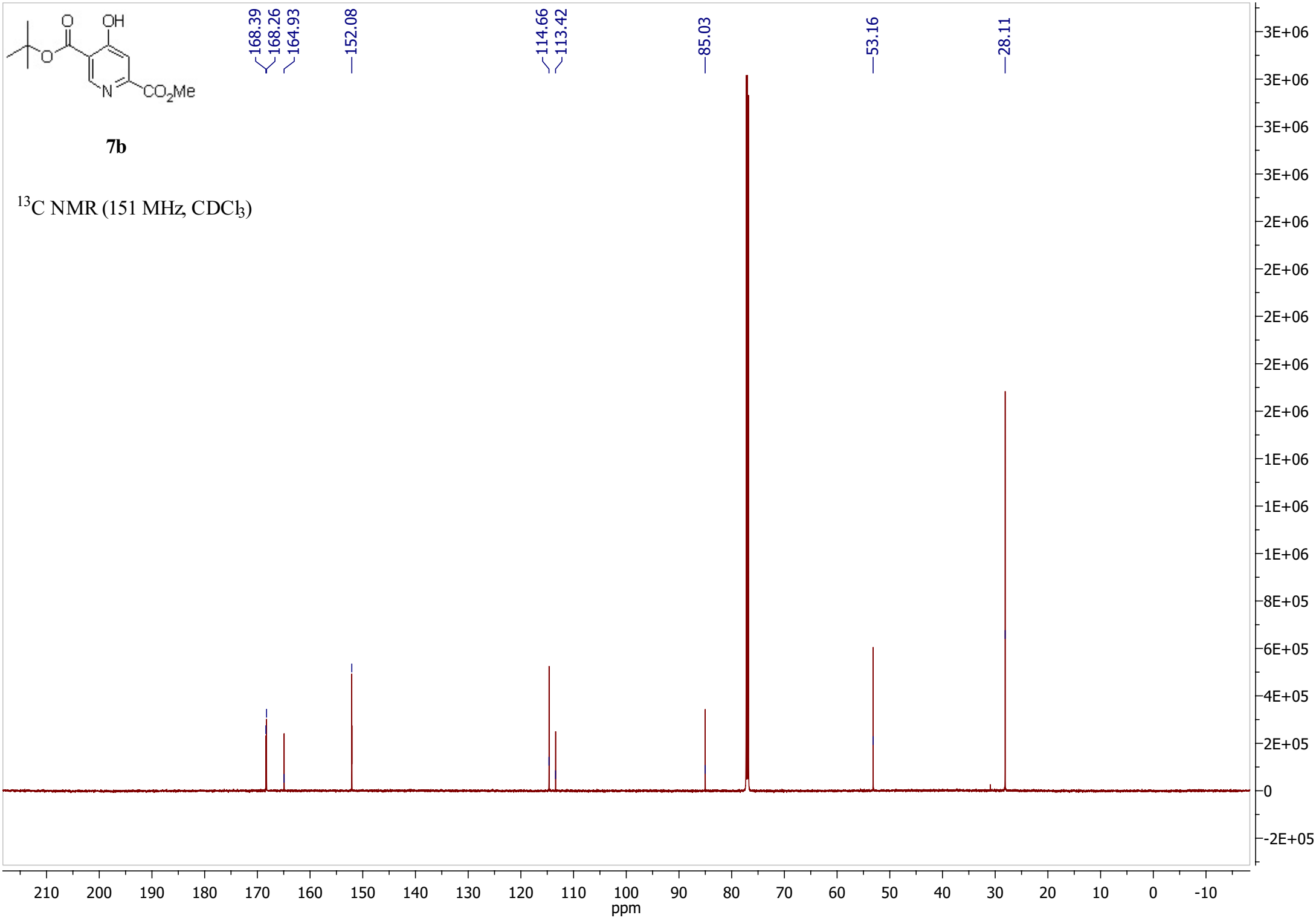
$^{13}$C NMR (126 MHz, $CDCl_3$)


11.49
8.95
7.69
4.01
1.64
O
OH
O
N
CO2Me
7b
1H NMR (500 MHz, CDCl3)
0.82
0.83
0.83
2.88
8.26
ppm



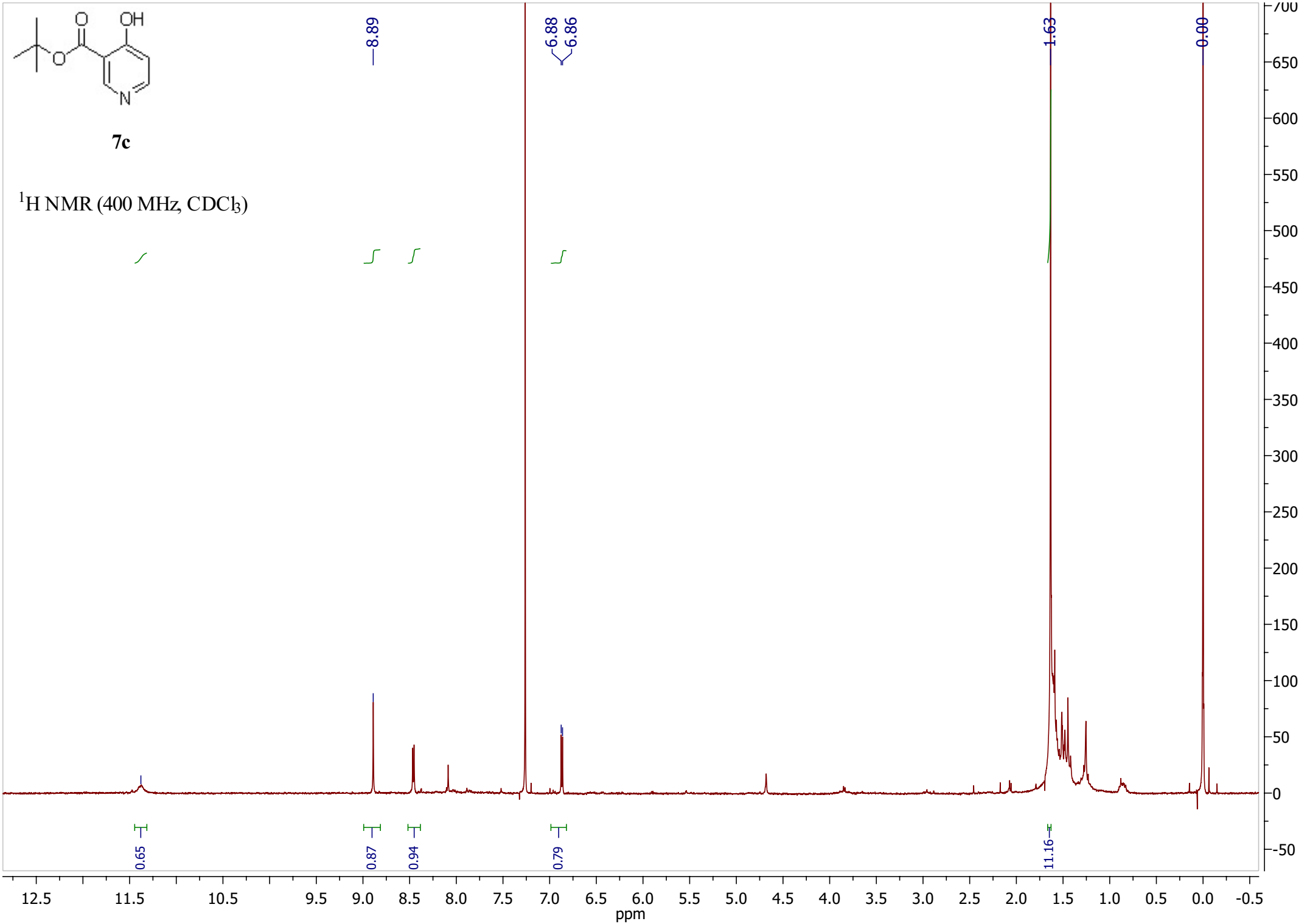

**7b**

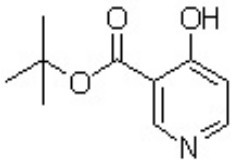
$^1$H NMR (500 MHz, DMSO-$d_6$)




**7b**

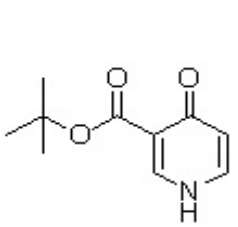
$^{13}C$ NMR (151 MHz, $CDCl_3$)


OH
O
O
N
7c
1H NMR (400 MHz, CDCl3)
8.89
6.88
6.86
1.63
0.00
0.65
0.87
0.94
0.79
11.16
ppm



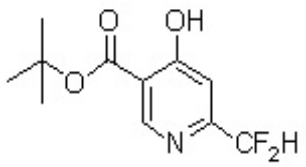

**7c**

$^1$H NMR (500 MHz, DMSO-$d_6$)



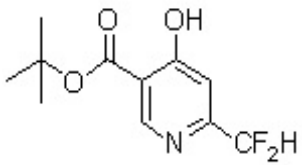
**7c**

$^{13}$C NMR (126 MHz, $CDCl_3$)



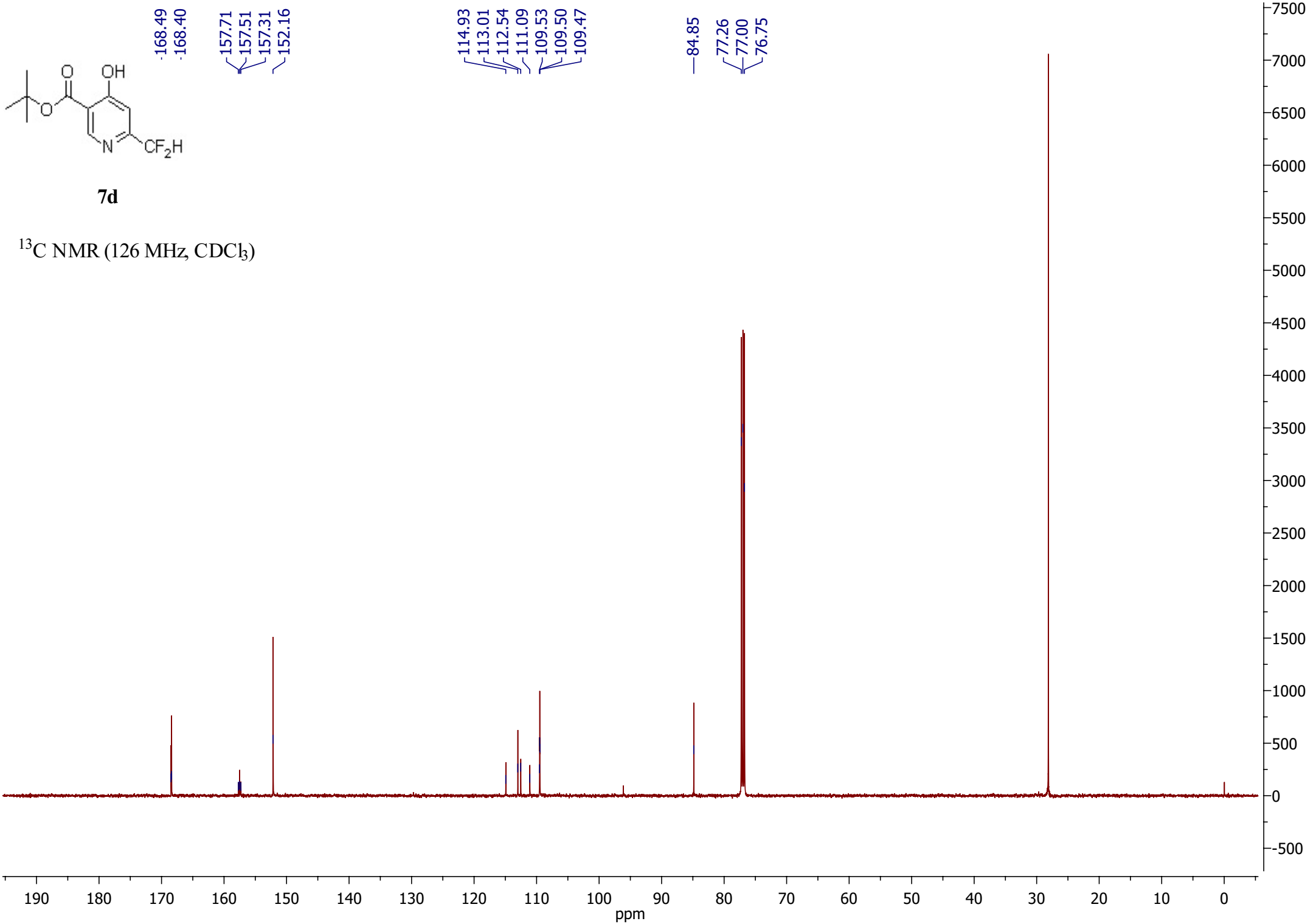

**7d**

$^1$H NMR (400 MHz, $CDCl_3$)



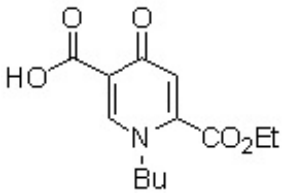

**7d**

$^{19}F$ NMR (471 MHz, $CDCl_3$)



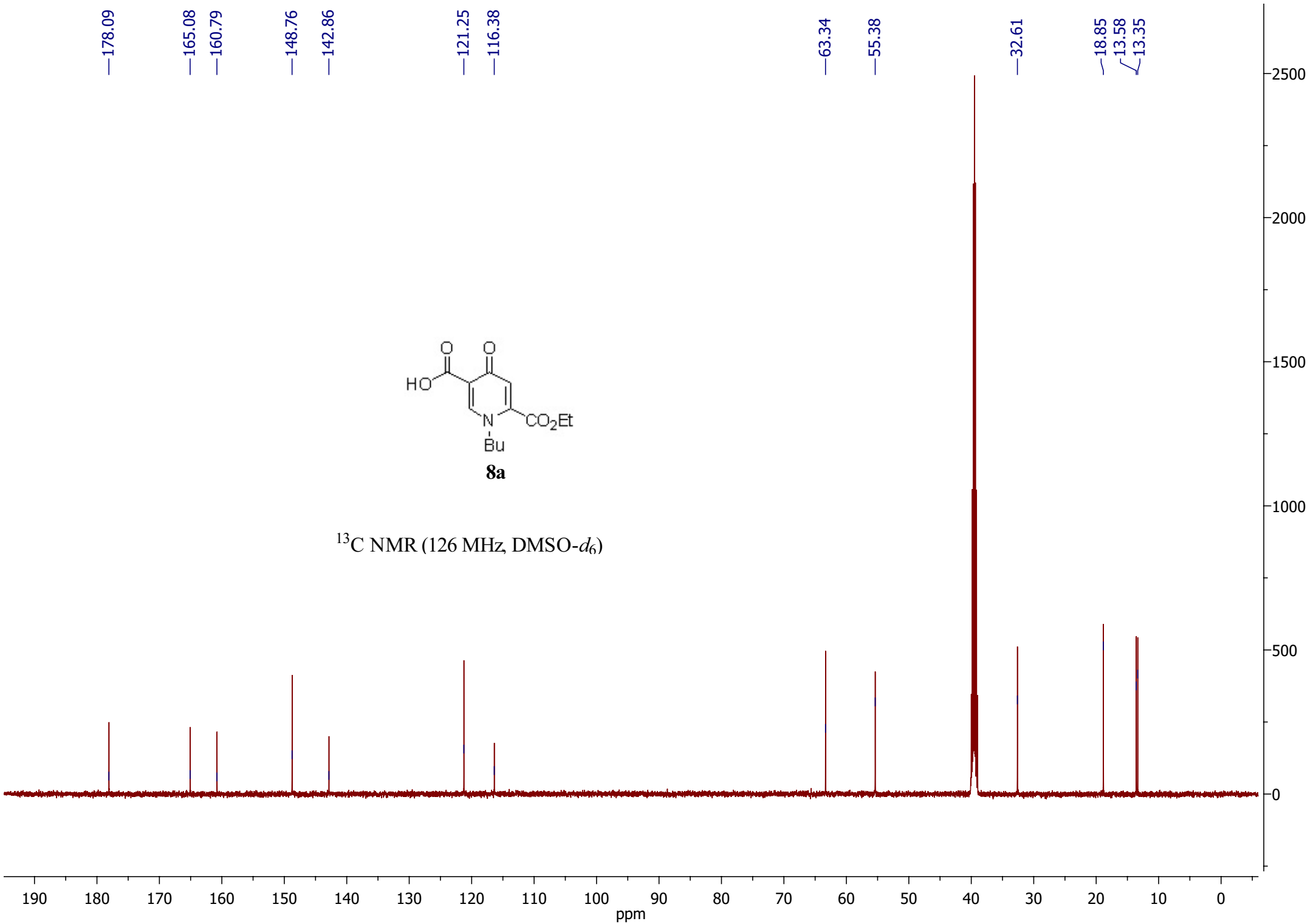

**7d**

$^{13}C$ NMR (126 MHz, $CDCl_3$)




**8a**

$^{1}$H NMR (500 MHz, DMSO-$d_6$)

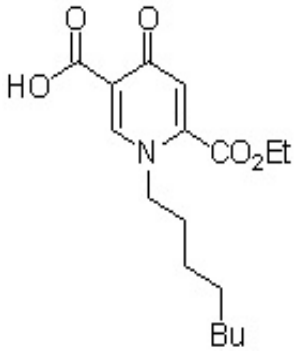






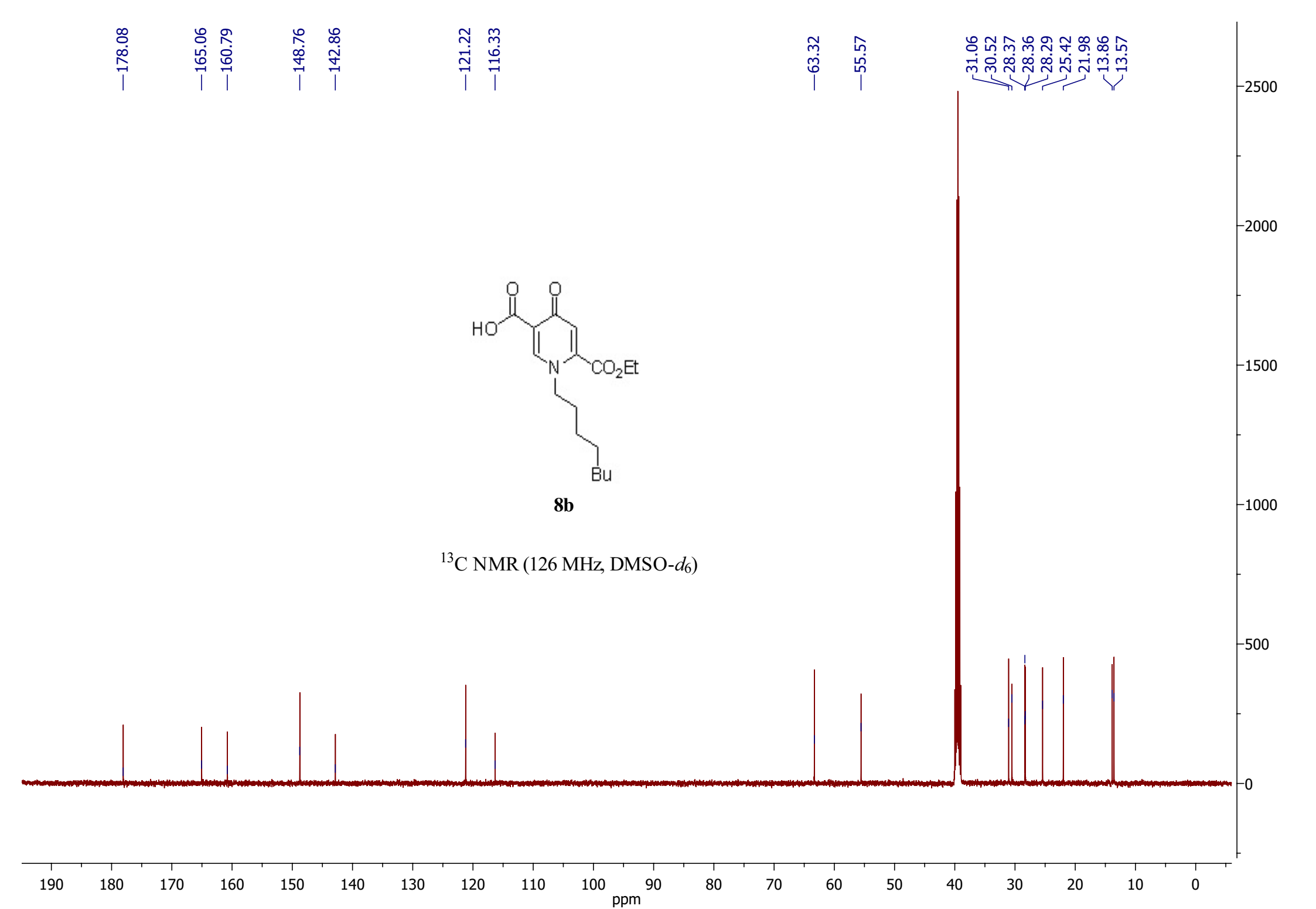
**8a**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



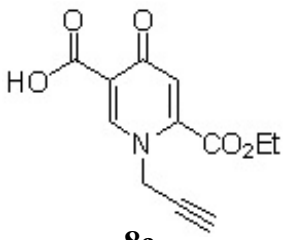

**8b**

$^{1}$H NMR (500 MHz, DMSO-$d_6$)



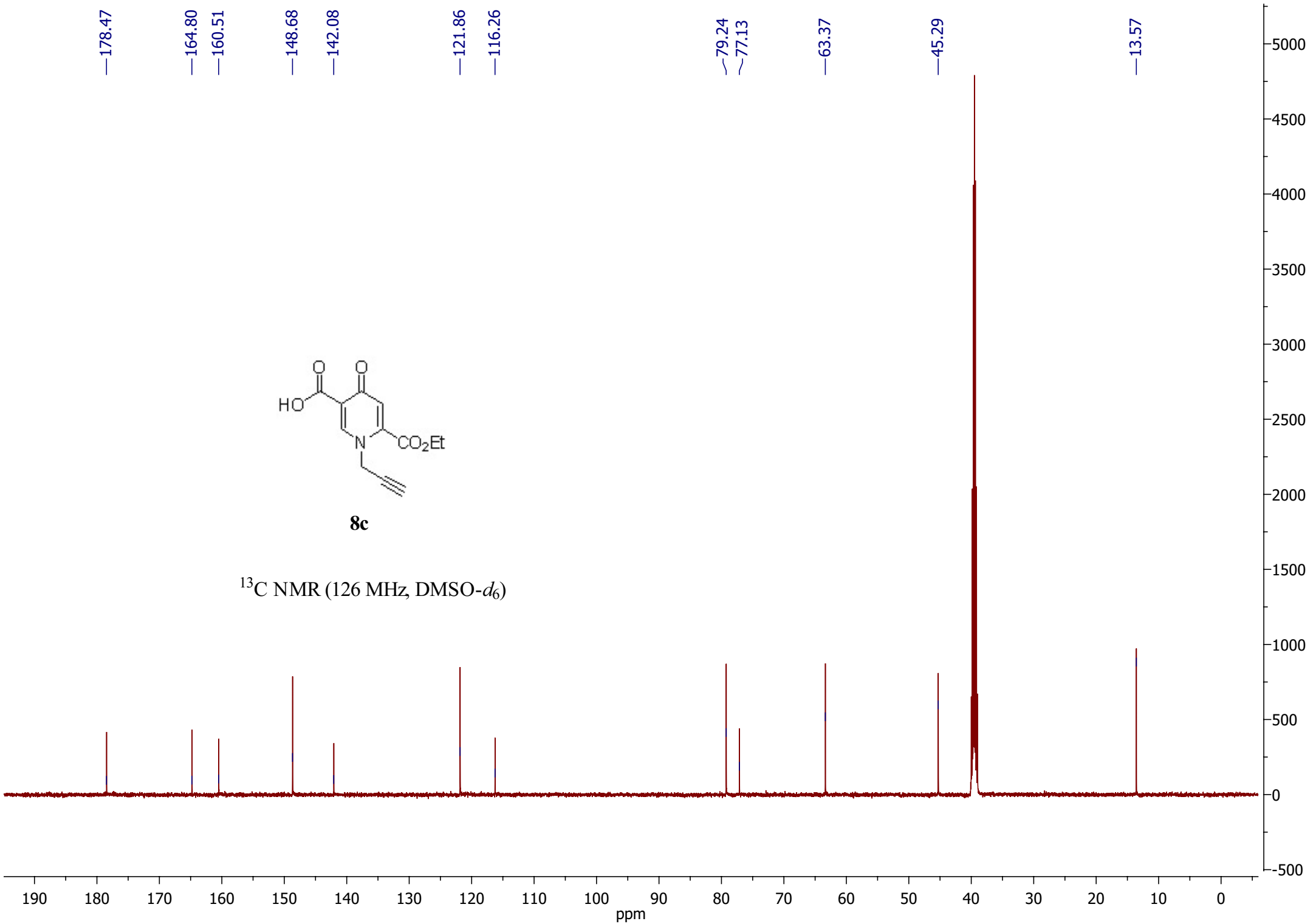

**8b**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



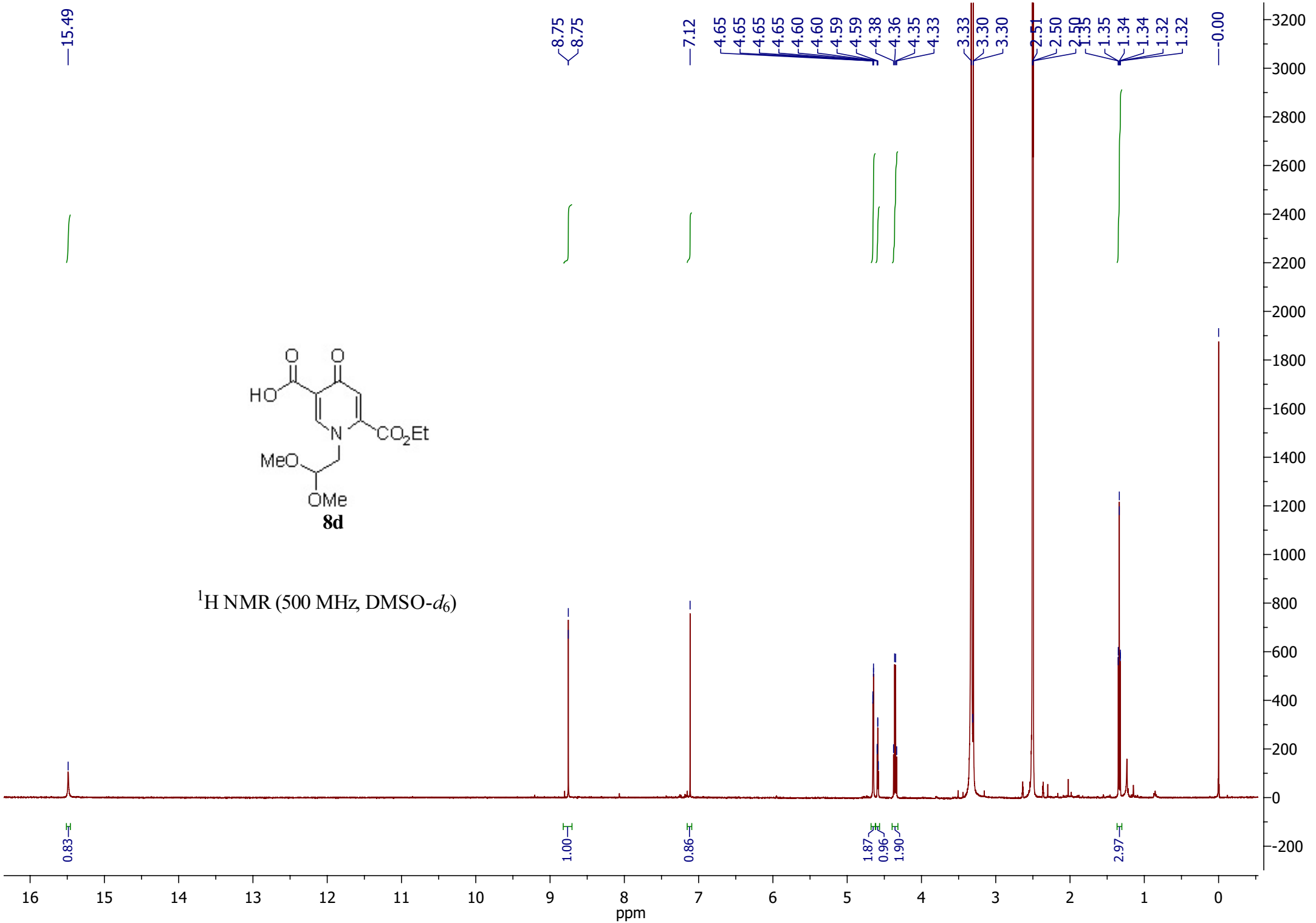

**8c**

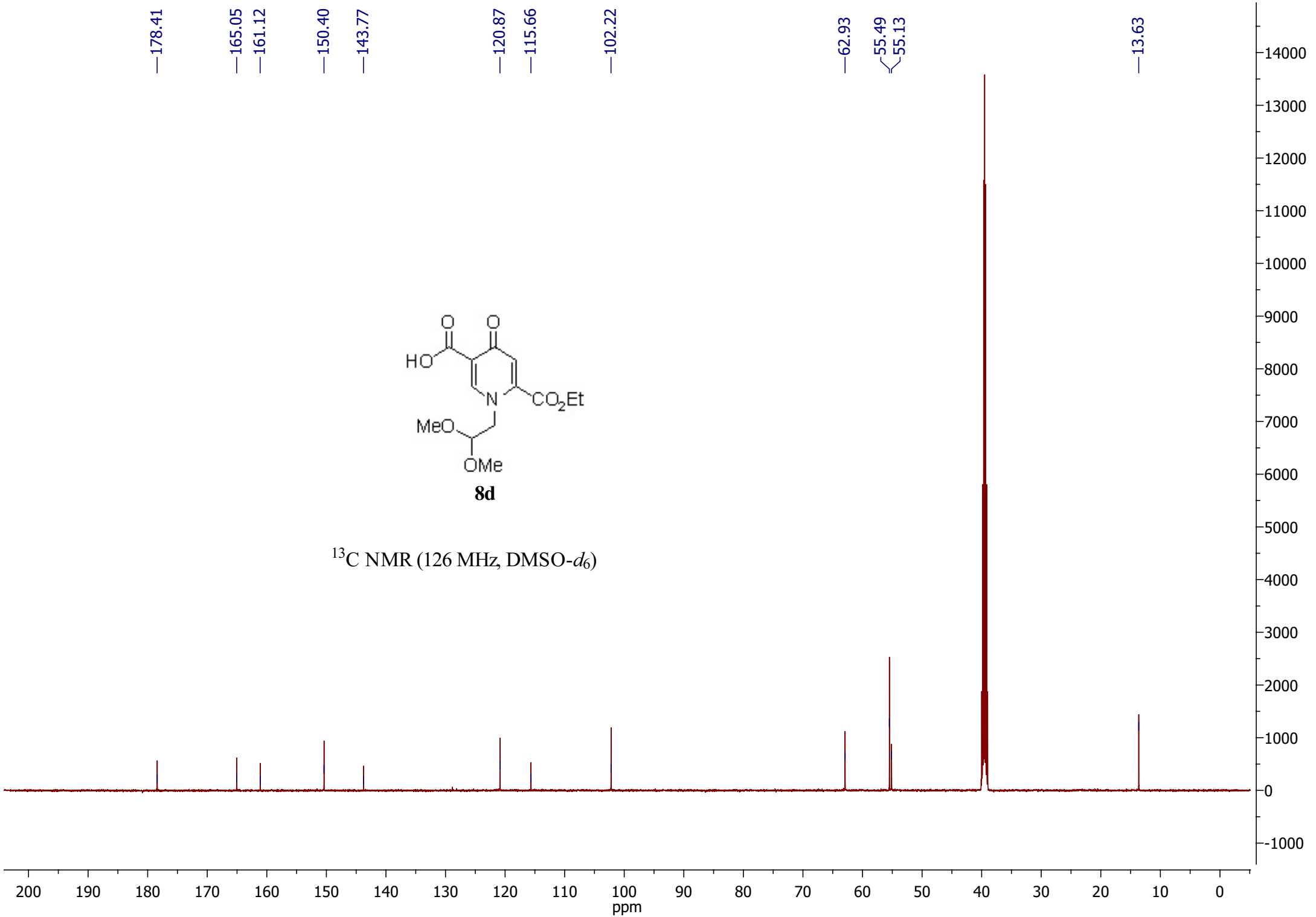
$^{1}$H NMR (500 MHz, DMSO-$d_6$)




**8c**

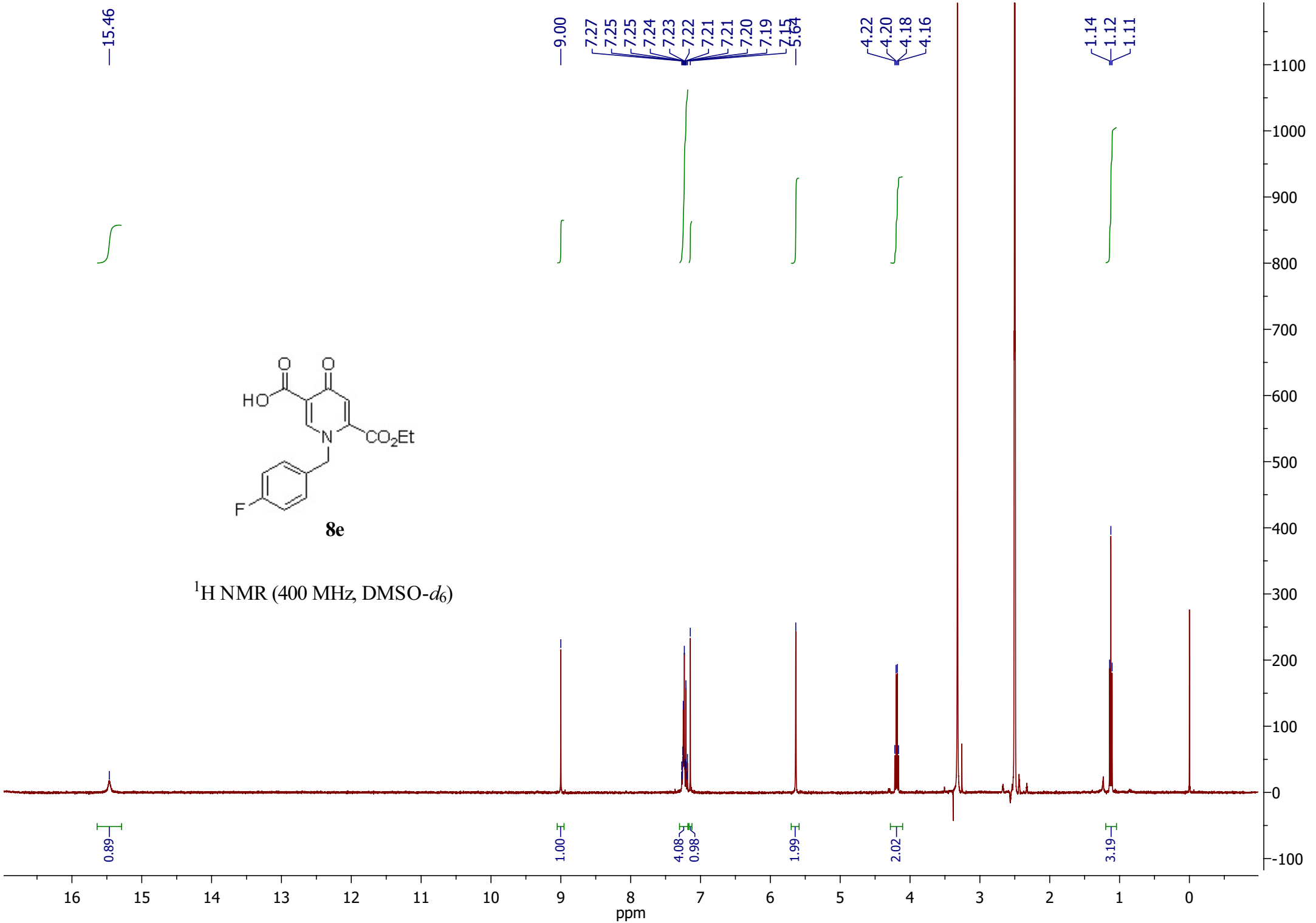
$^{13}$C NMR (126 MHz, DMSO-$d_6$)


15.49
8.75
8.75
7.12
4.65
4.65
4.65
4.65
4.60
4.60
4.59
4.59
4.38
4.36
4.35
4.33
3.33
3.30
3.30
2.51
2.50
2.50
1.35
1.35
1.34
1.34
1.32
1.32
-0.00
HO
O
O
N
CO2Et
MeO
OMe
8d
1H NMR (500 MHz, DMSO-d6)
0.83
1.00
0.86
1.87
0.96
1.90
2.97
ppm



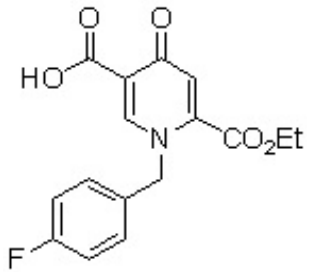

**8d**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



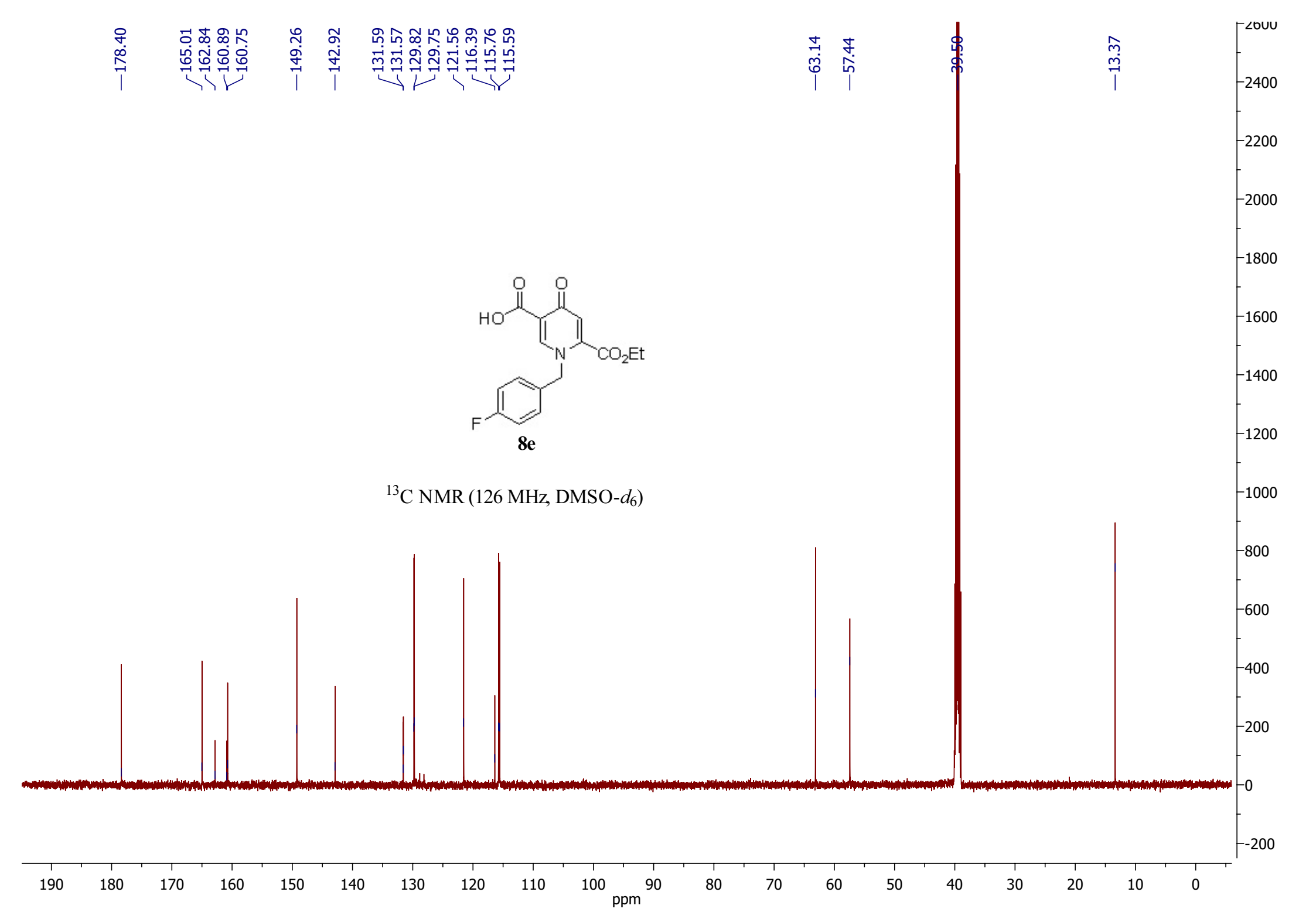

**8e**

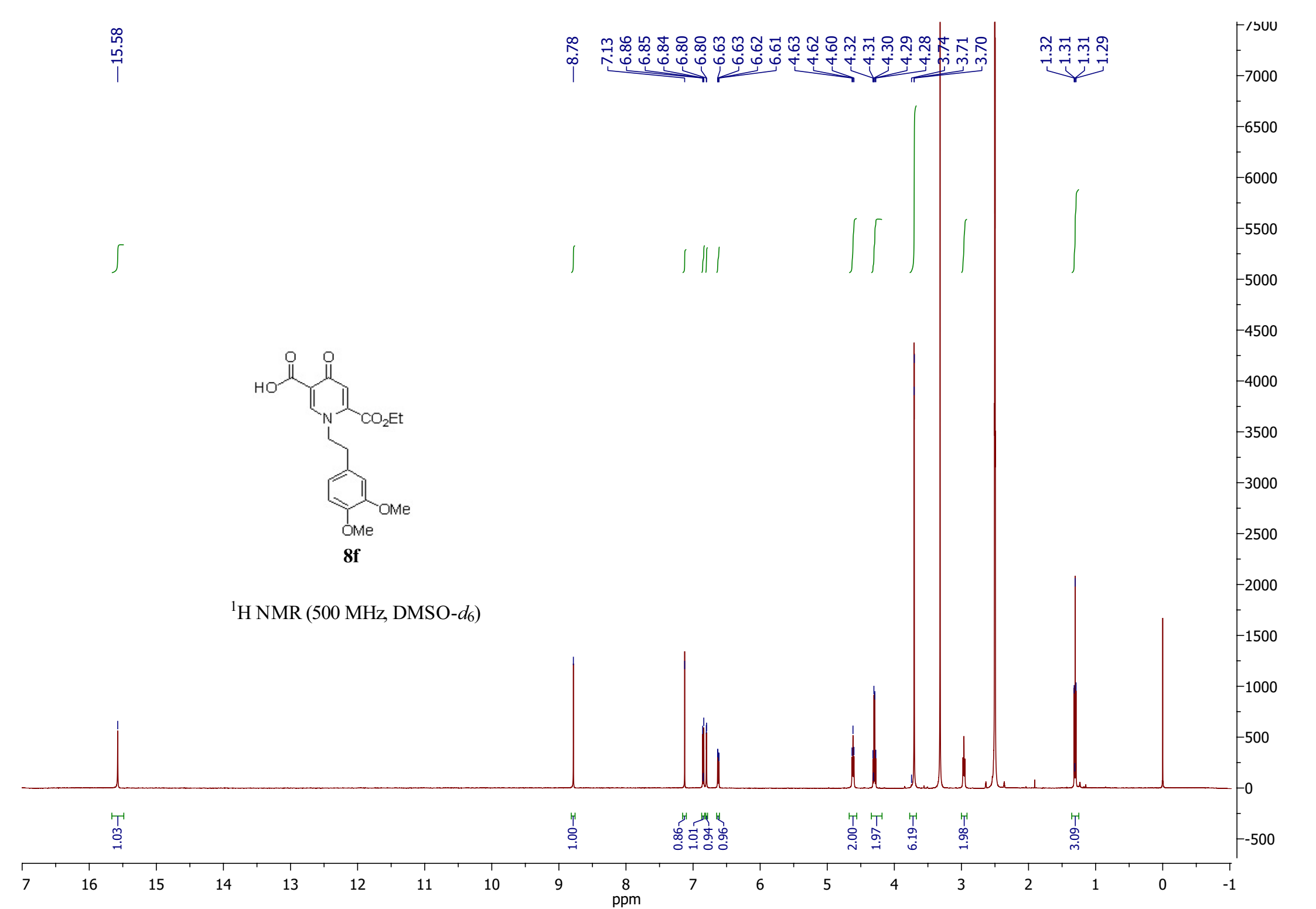
$^1$H NMR (400 MHz, DMSO-$d_6$)



**8e**

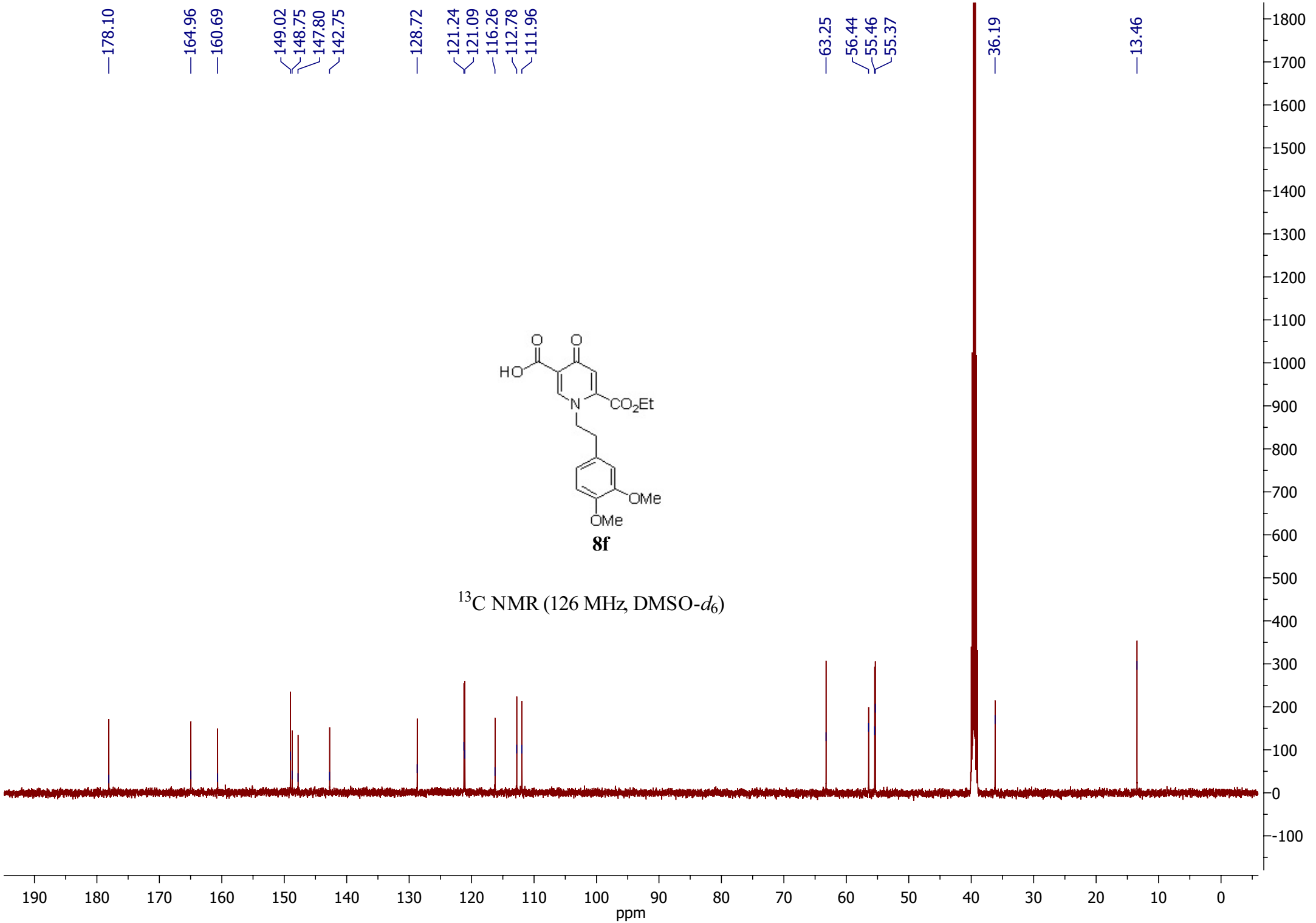
$^{19}$F NMR (376 MHz, DMSO-$d_6$)


178.40
165.01
162.84
160.89
160.75
149.26
142.92
131.59
131.57
129.82
129.75
121.56
116.39
115.76
115.59
63.14
57.44
39.50
13.37
HO
O
O
N
CO2Et
F
8e
13C NMR (126 MHz, DMSO-d6)
ppm



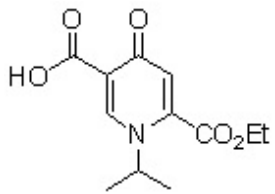

**8f**

$^1$H NMR (500 MHz, DMSO-$d_6$)



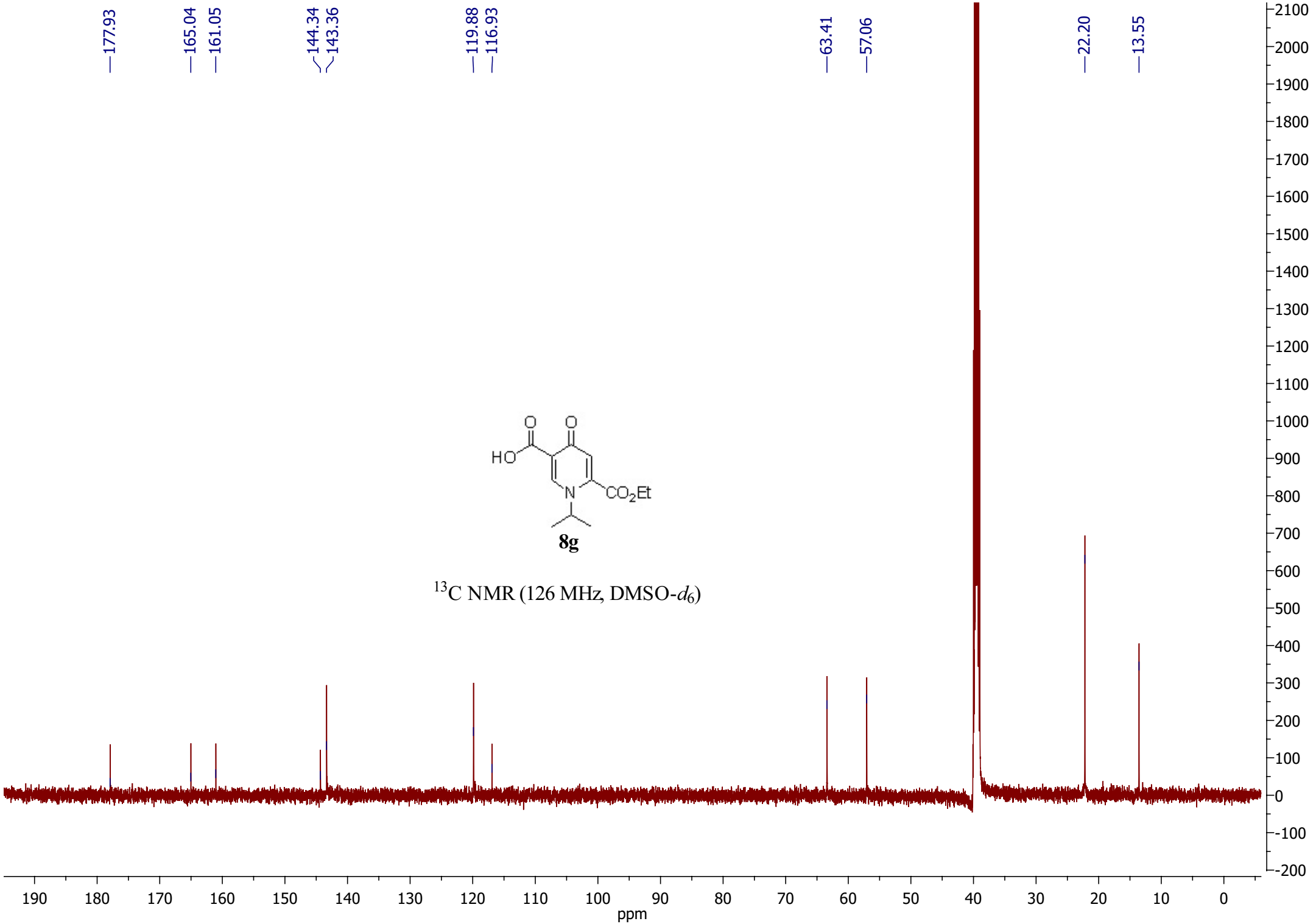

**8f**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



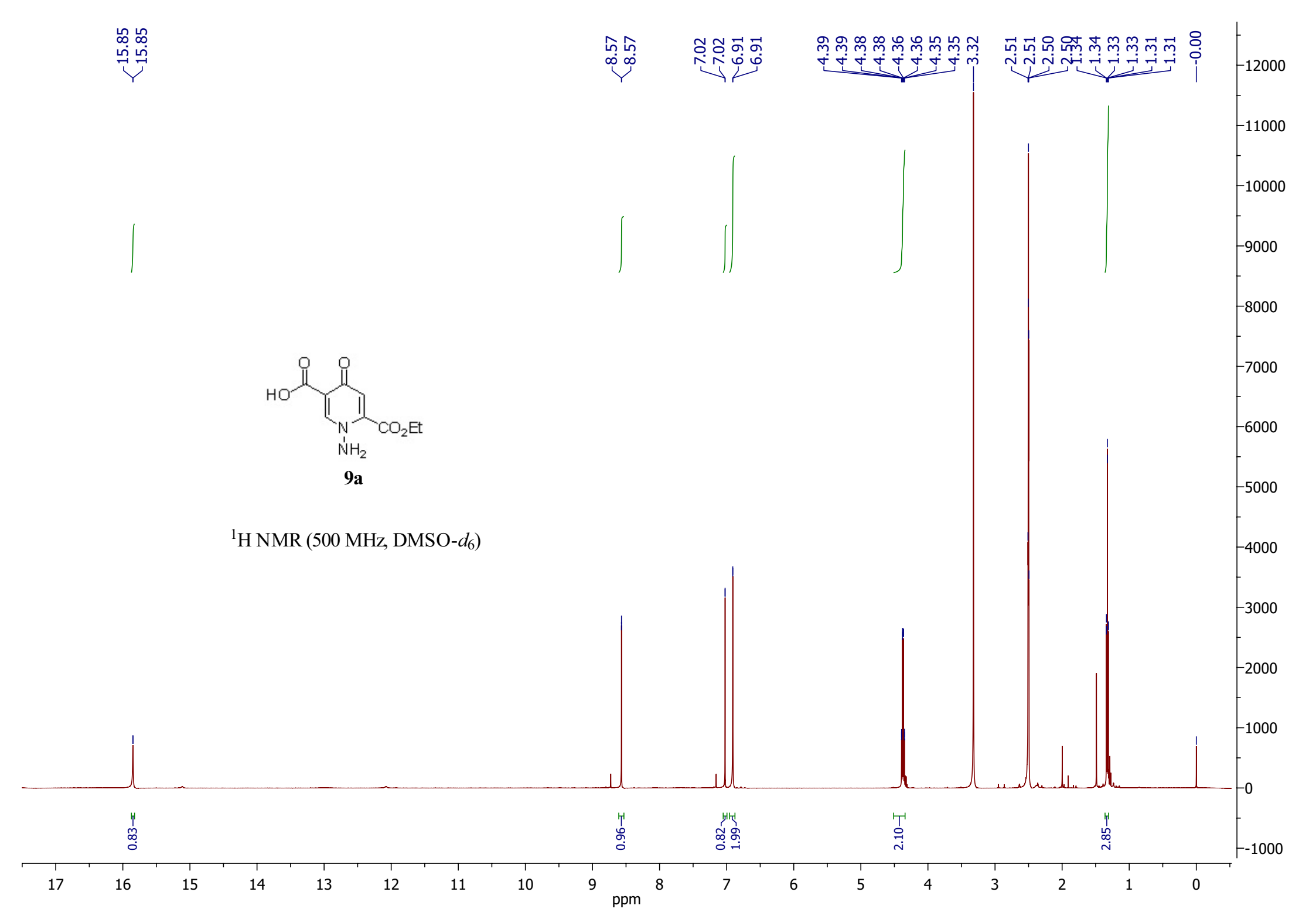
**8g**

$^1$H NMR (500 MHz, DMSO-$d_6$)



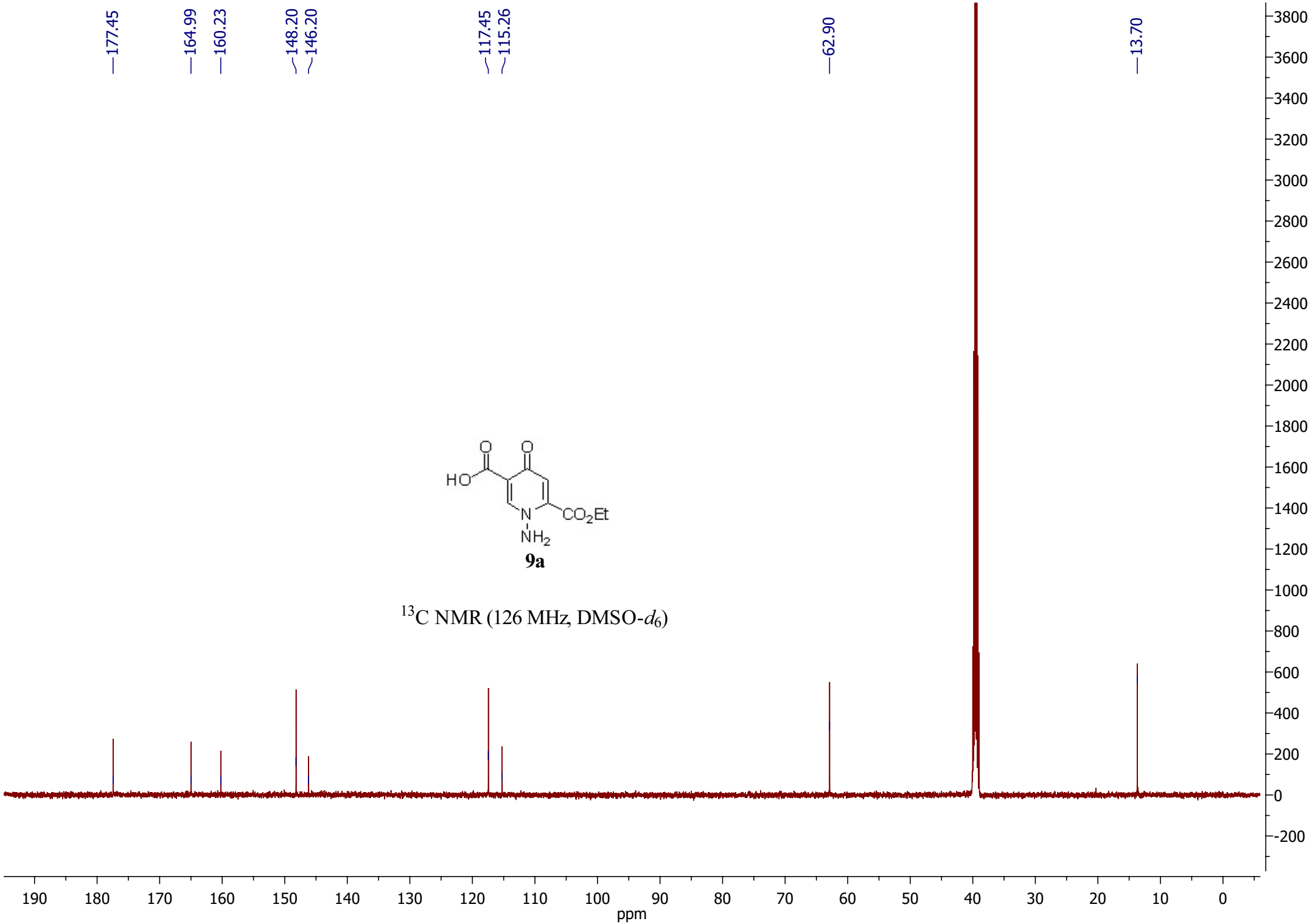

**8g**

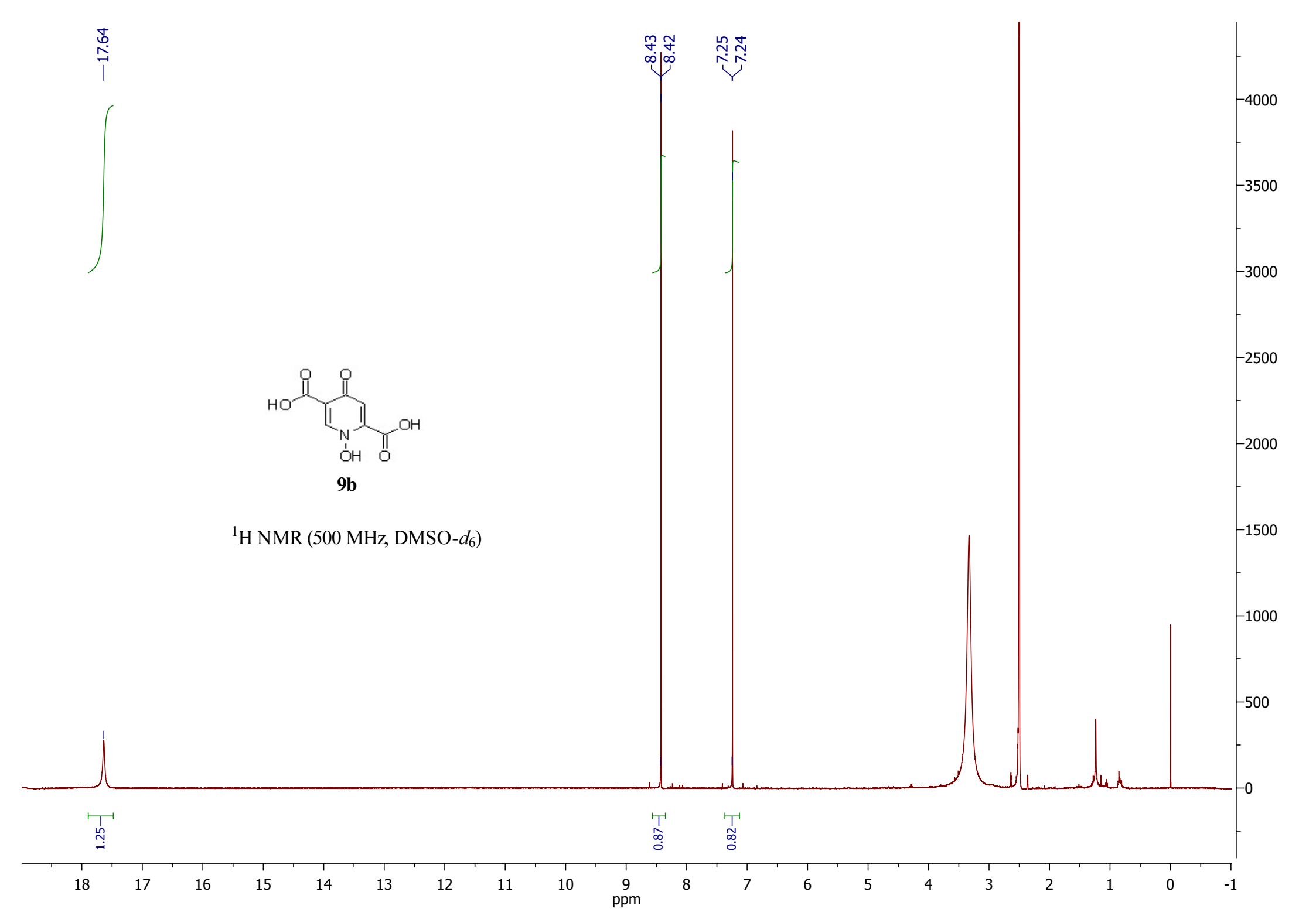
$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**9a**

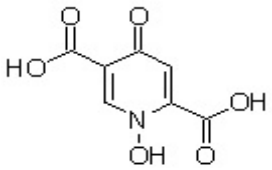
$^{1}$H NMR (500 MHz, DMSO-$d_6$)


177.45
164.99
160.23
148.20
146.20
117.45
115.26
62.90
13.70
HO
O
O
N
NH2
CO2Et
9a
13C NMR (126 MHz, DMSO-d6)
ppm



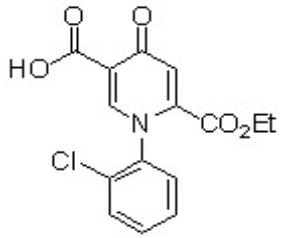

**9b**

$^1$H NMR (500 MHz, DMSO-$d_6$)



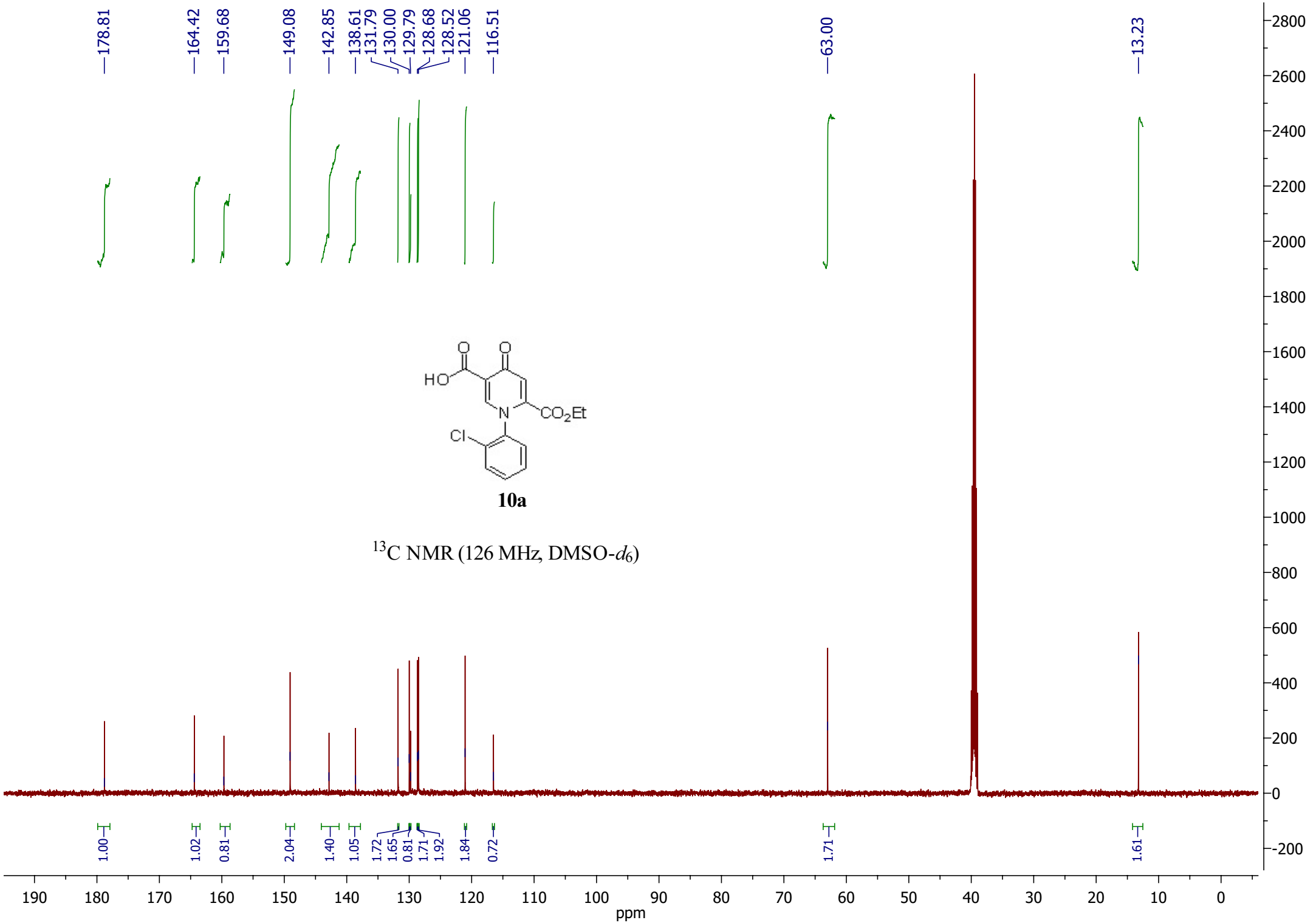
**9b**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



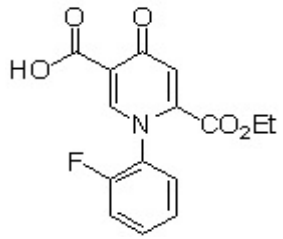
**10a**

$^1$H NMR (400 MHz, DMSO-$d_6$)



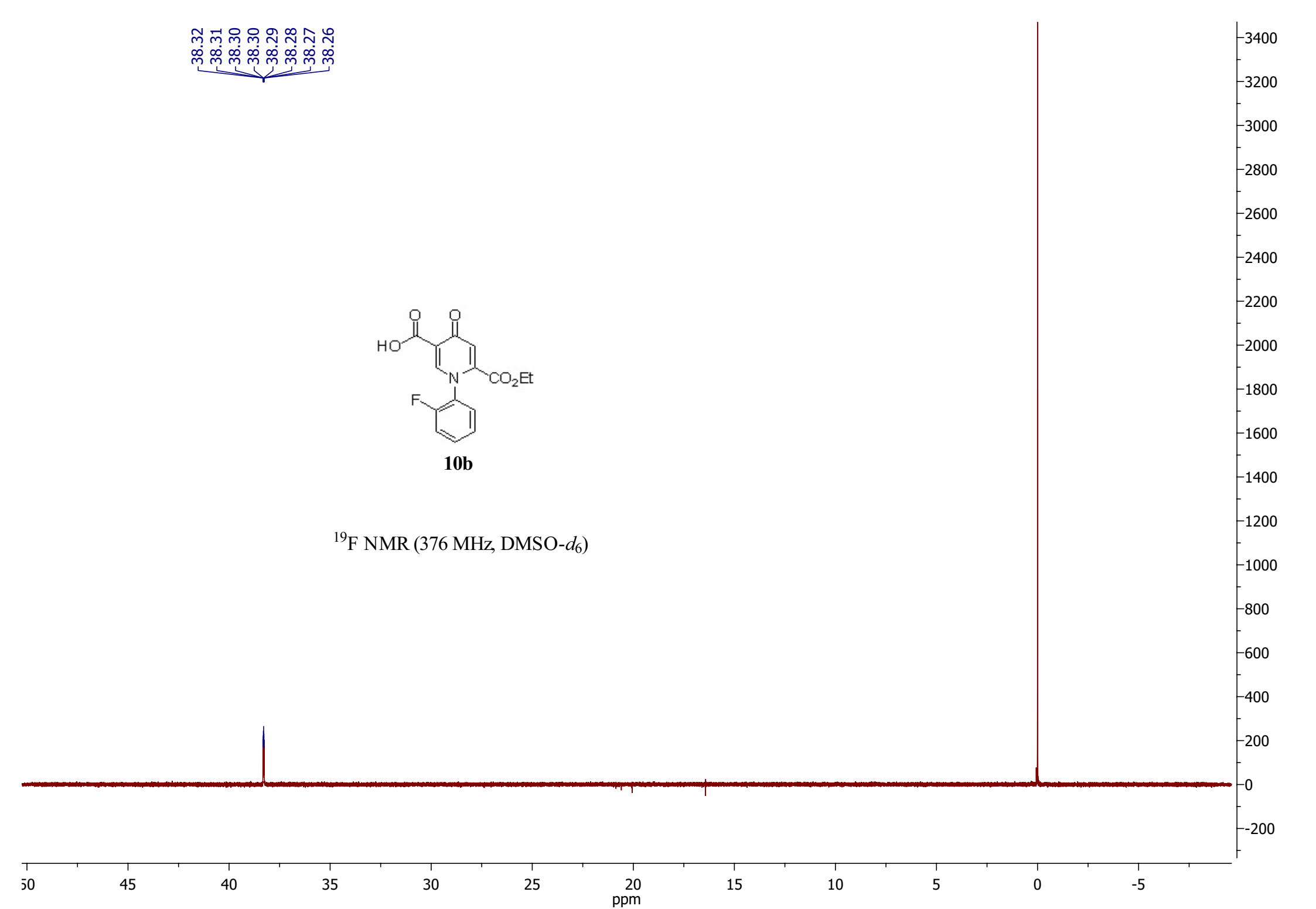

**10a**

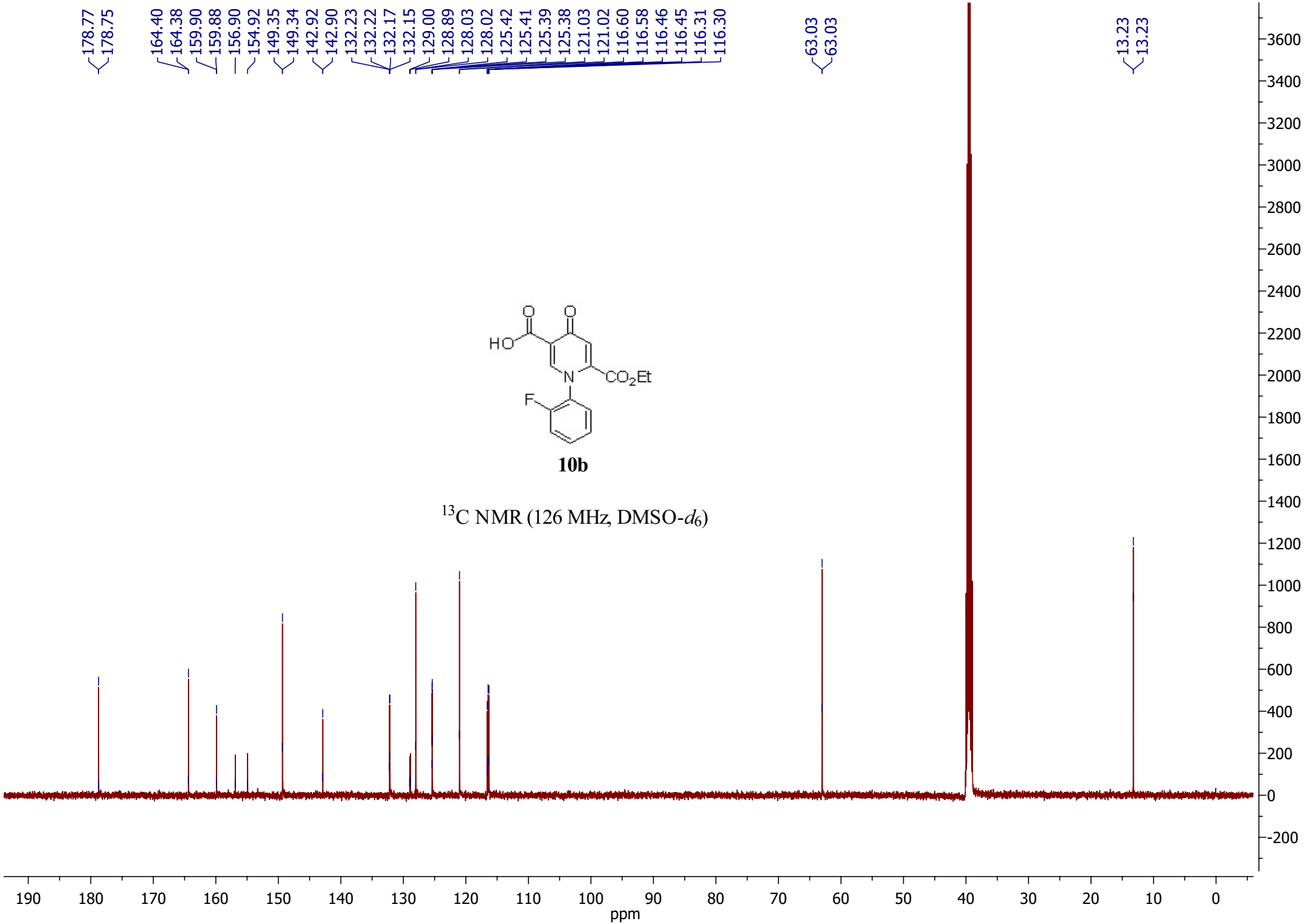
$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**10b**

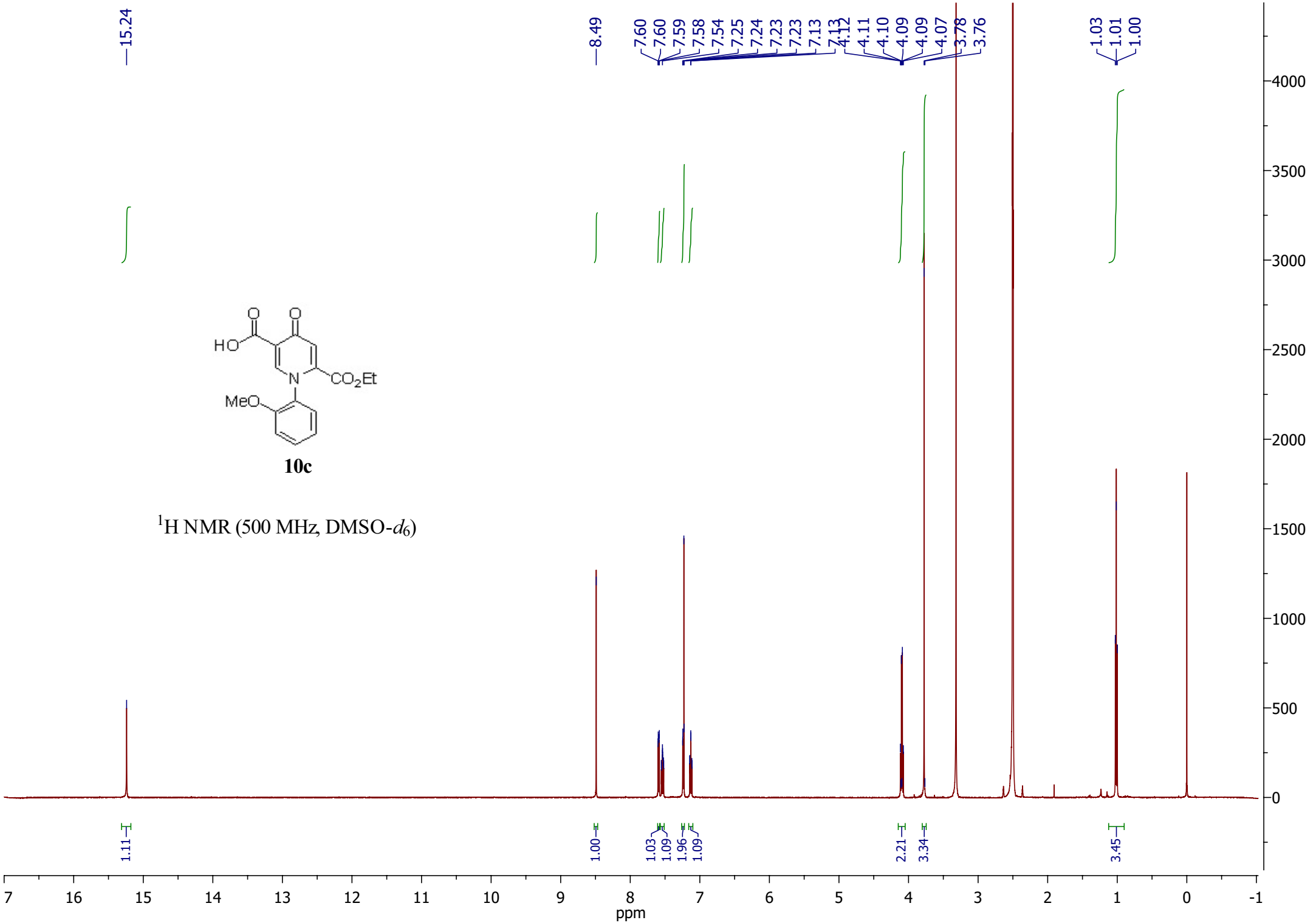
$^{1}$H NMR (400 MHz, DMSO-$d_6$)

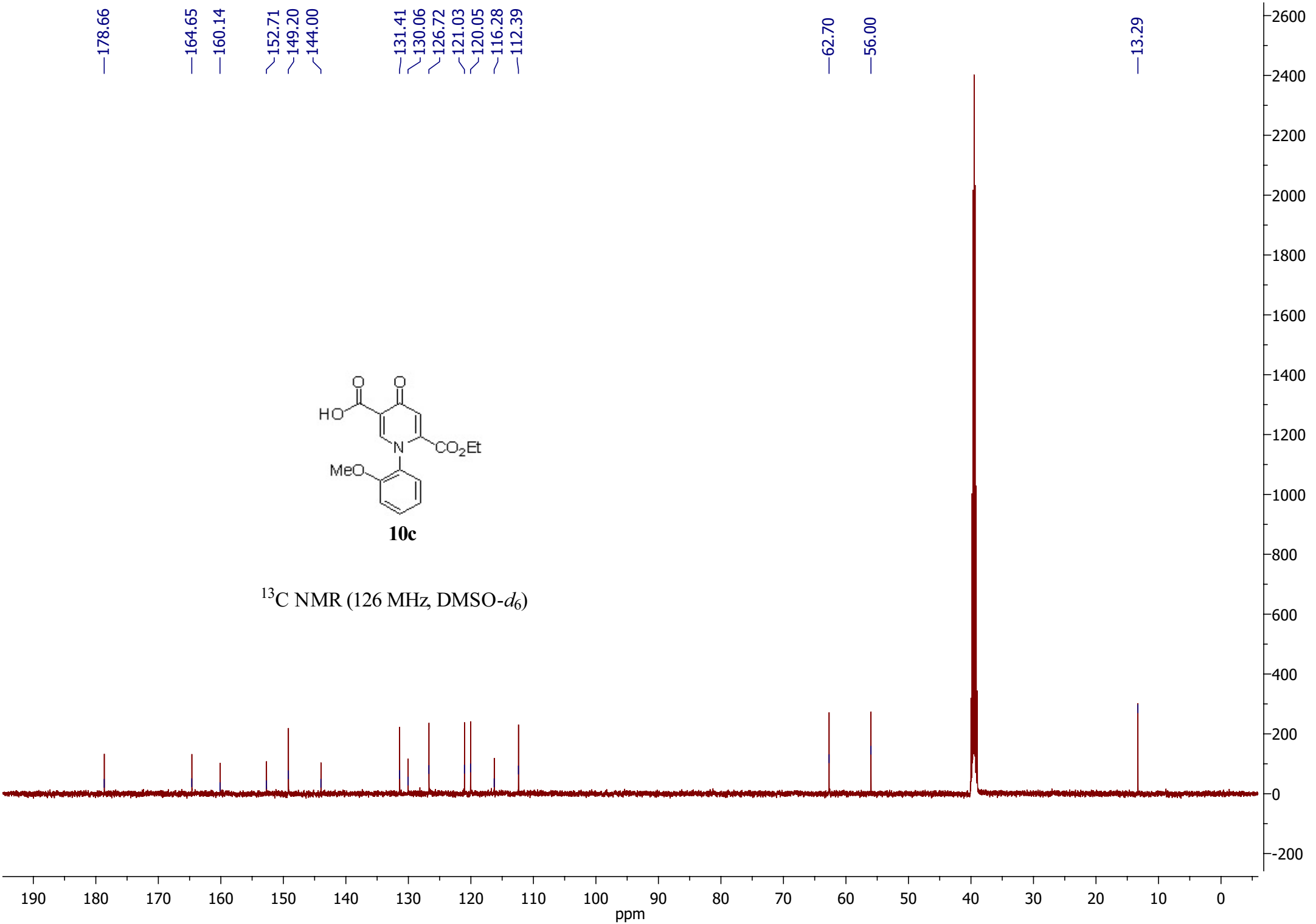

38.32
38.31
38.30
38.30
38.29
38.28
38.27
38.26
HO
O
O
N
CO2Et
F
10b
19F NMR (376 MHz, DMSO-d6)
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
50
45
40
35
30
25
20
15
10
5
0
-5
ppm




**10b**

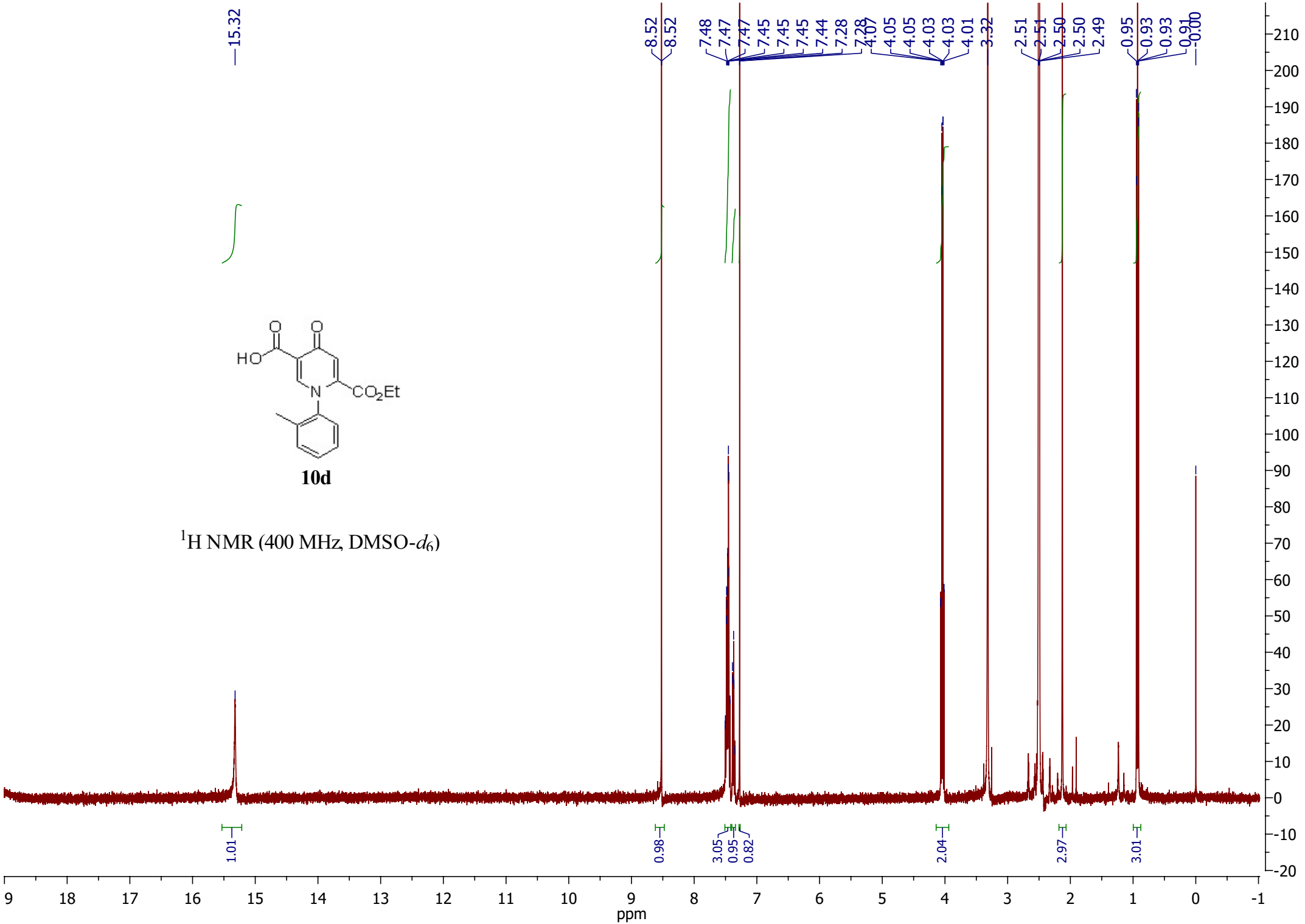
$^{13}$C NMR (126 MHz, DMSO-$d_6$)


15.24
8.49
7.60
7.60
7.59
7.58
7.54
7.25
7.24
7.23
7.23
7.13
7.13
4.12
4.11
4.10
4.09
4.09
4.07
3.78
3.76
1.03
1.01
1.00
HO
O
O
N
CO2Et
MeO
10c
1H NMR (500 MHz, DMSO-d6)
1.11
1.00
1.03
1.09
1.96
1.09
2.21
3.34
3.45
ppm



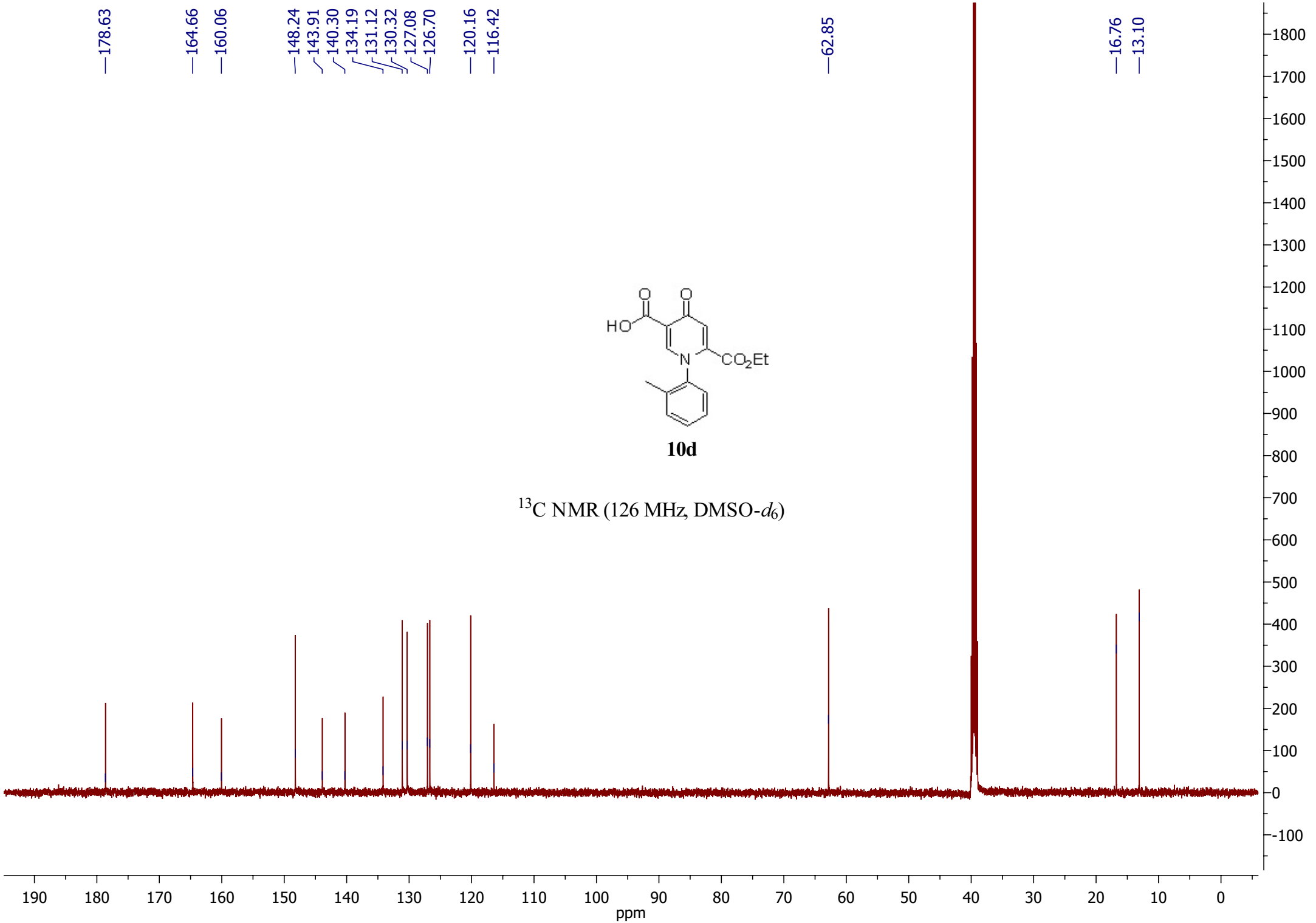

**10c**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



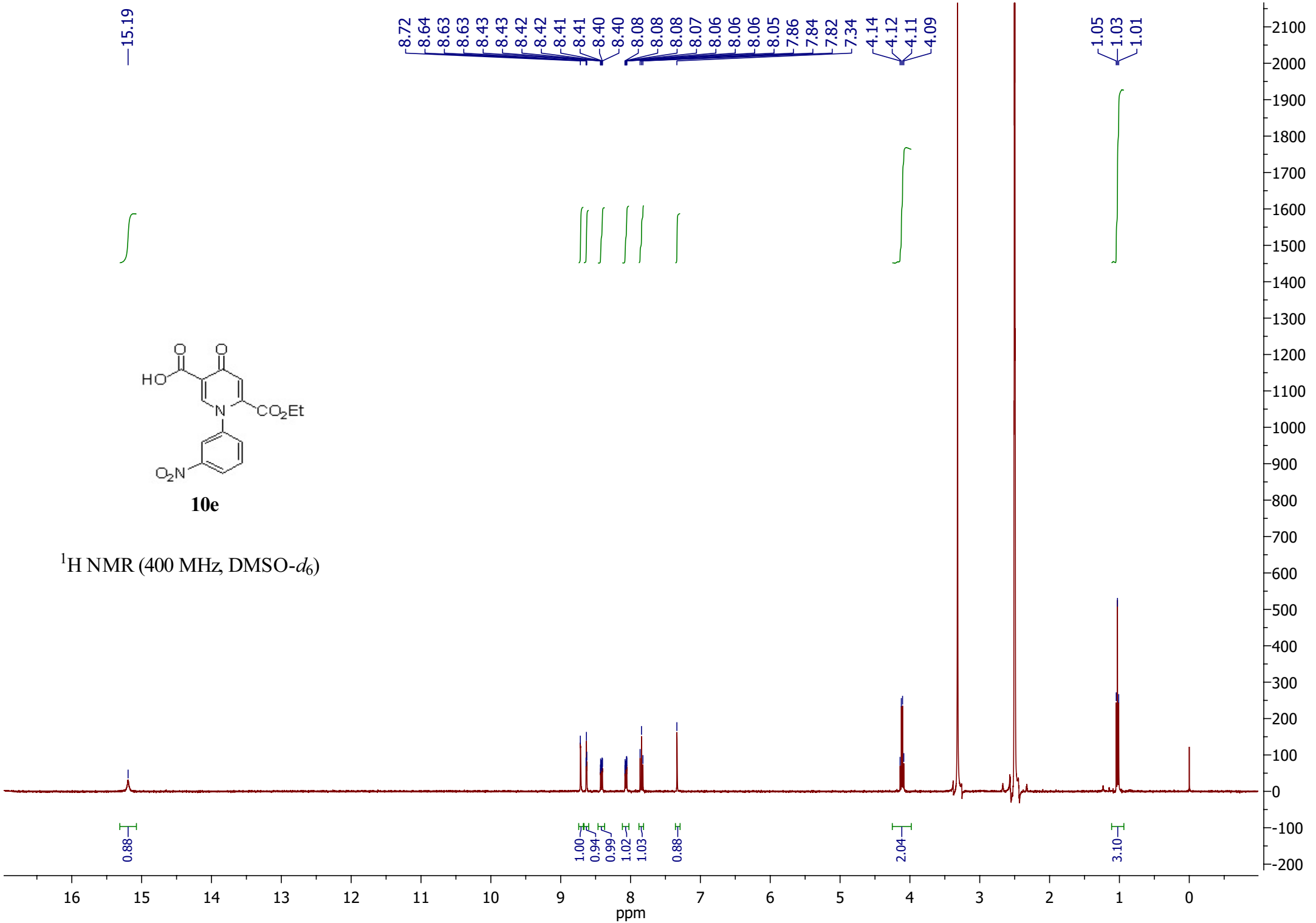

**10d**

$^1$H NMR (400 MHz, DMSO-$d_6$)



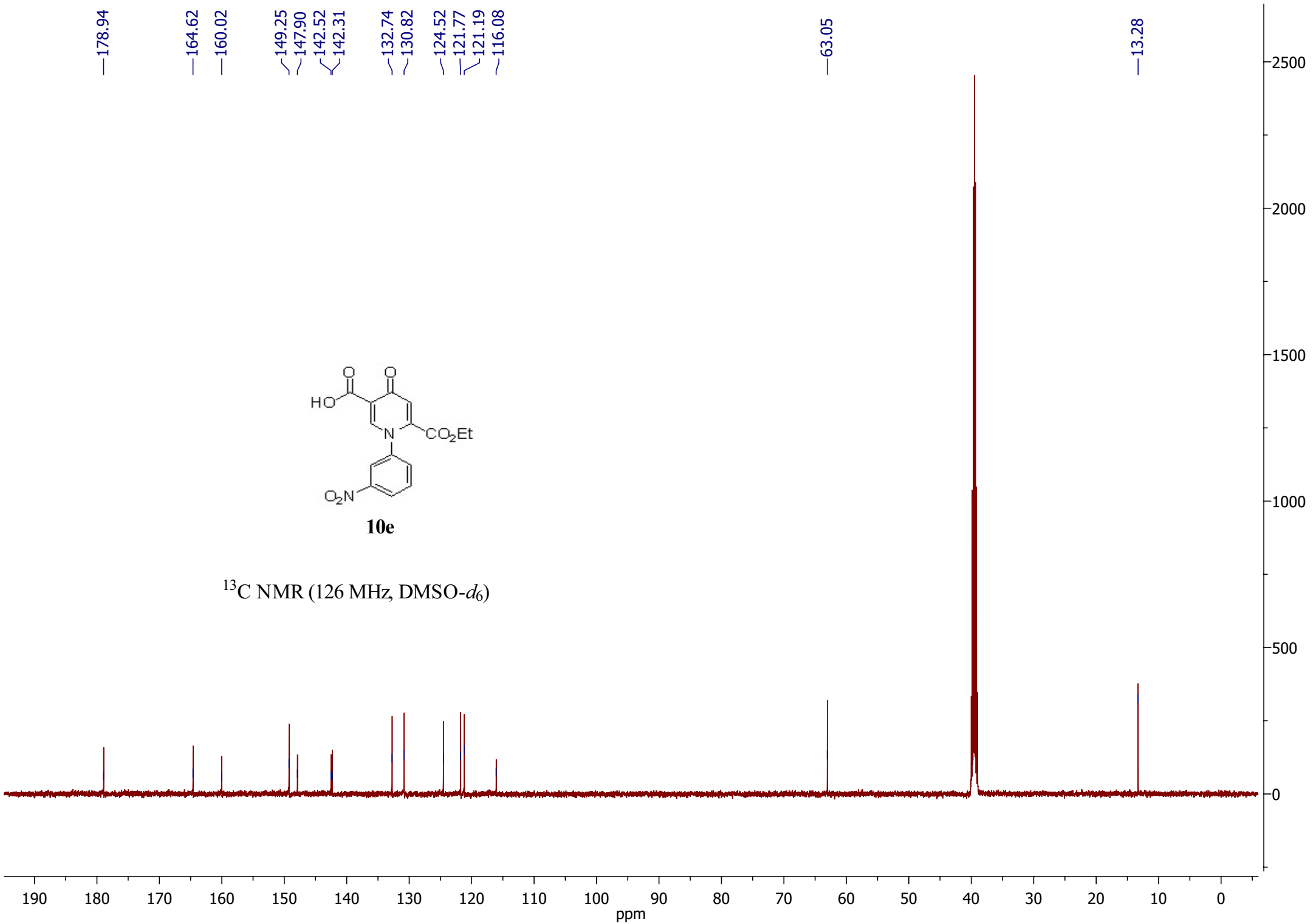

**10d**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



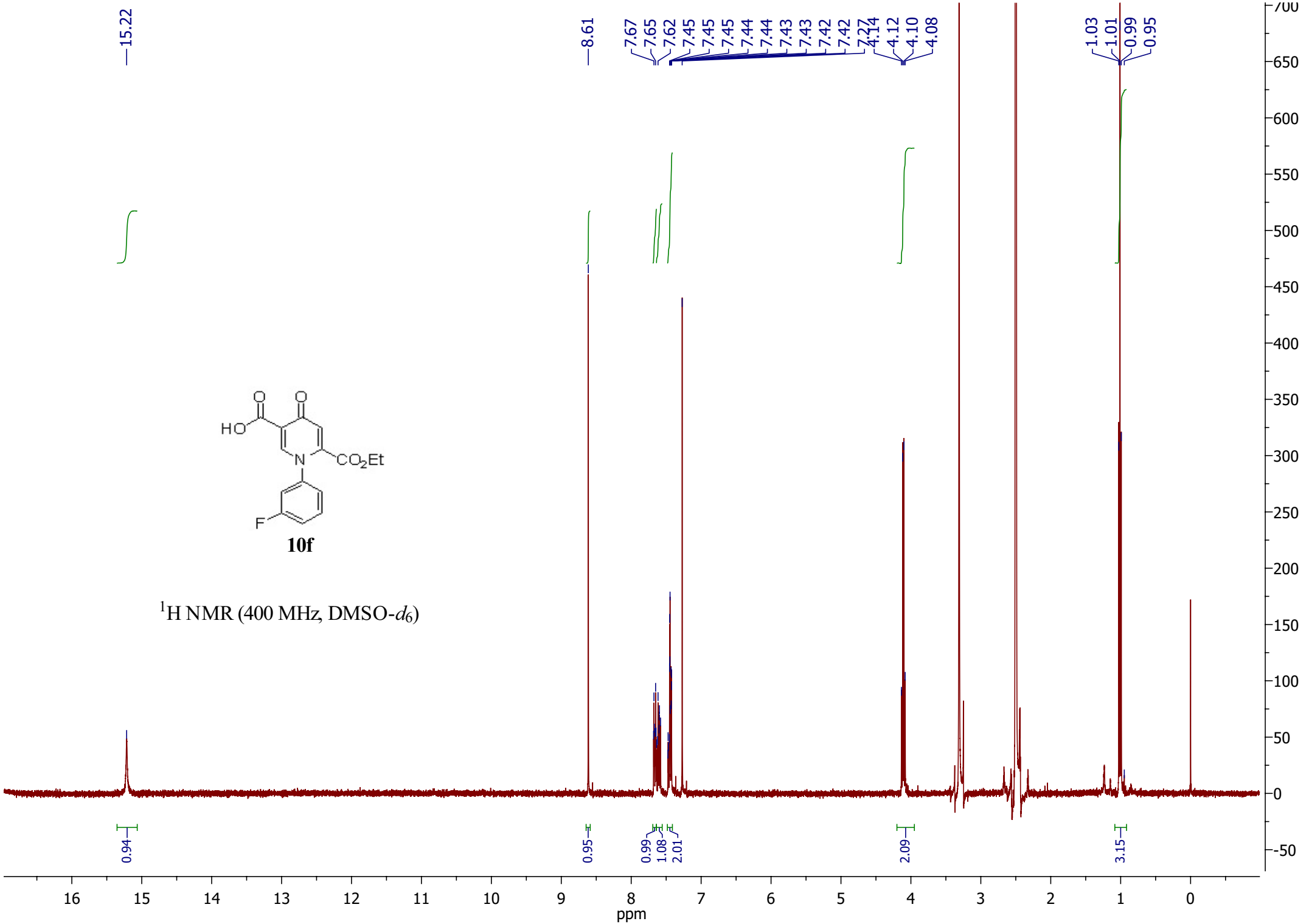

**10e**

$^1$H NMR (400 MHz, DMSO-$d_6$)



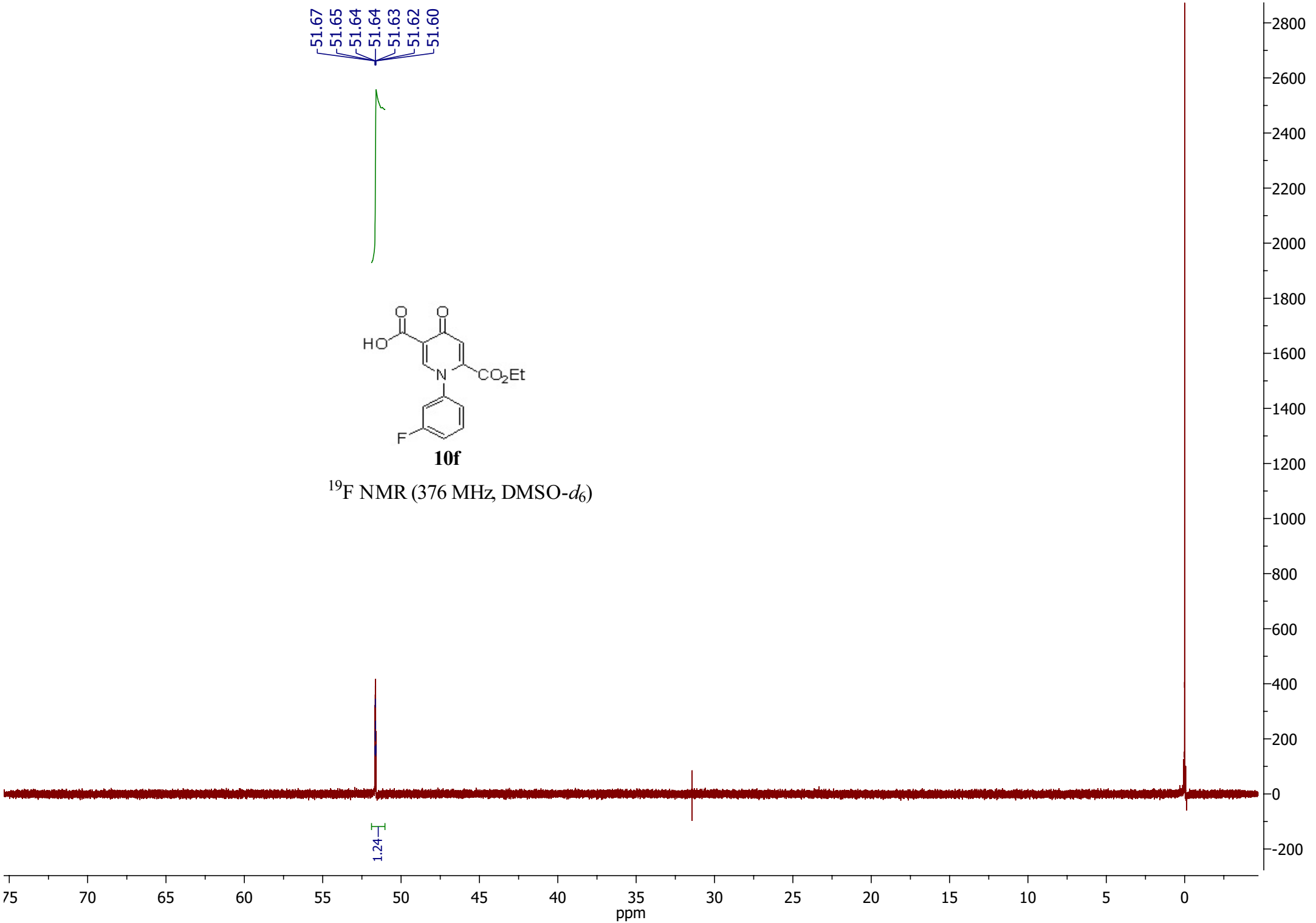

**10e**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



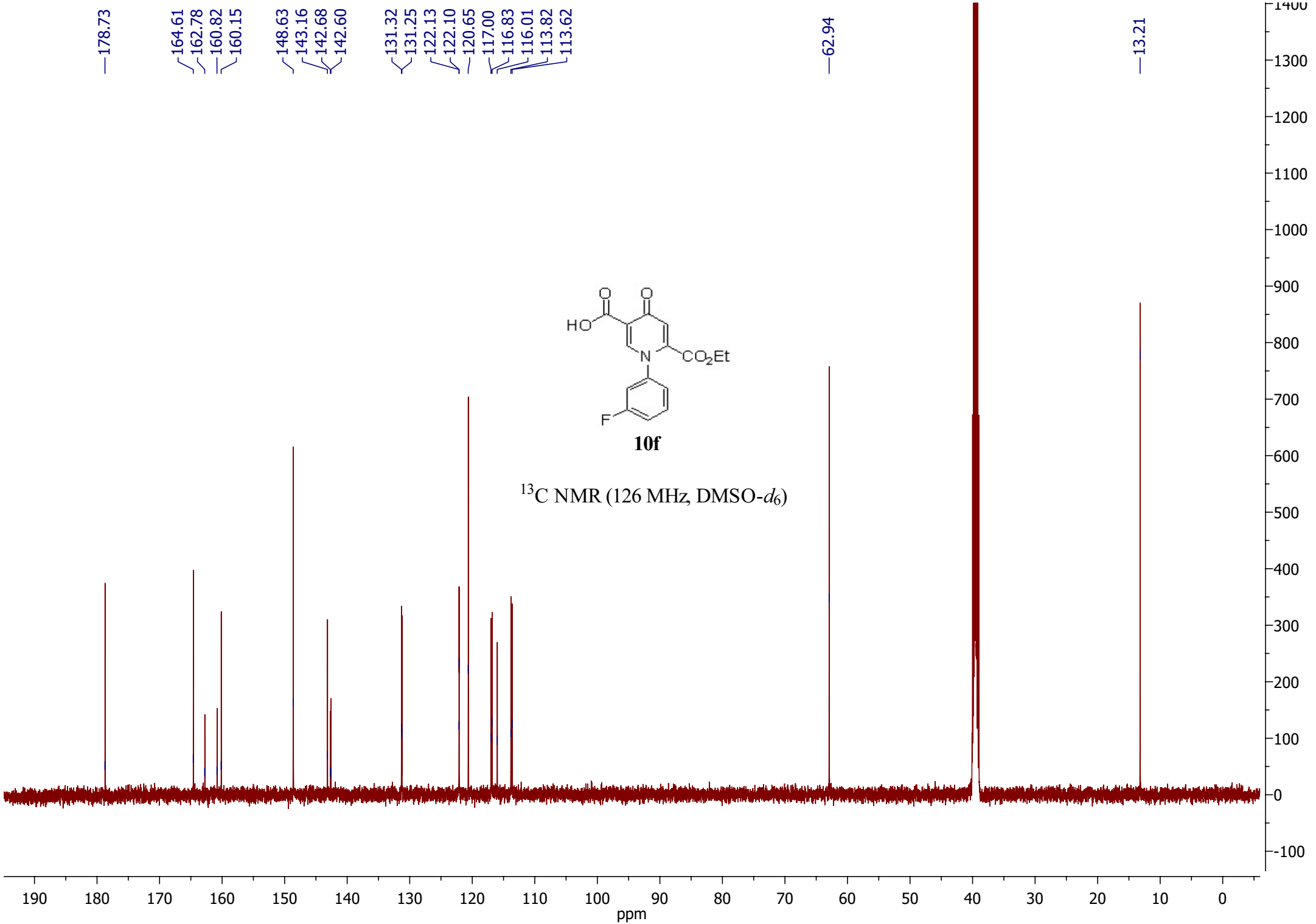

**10f**

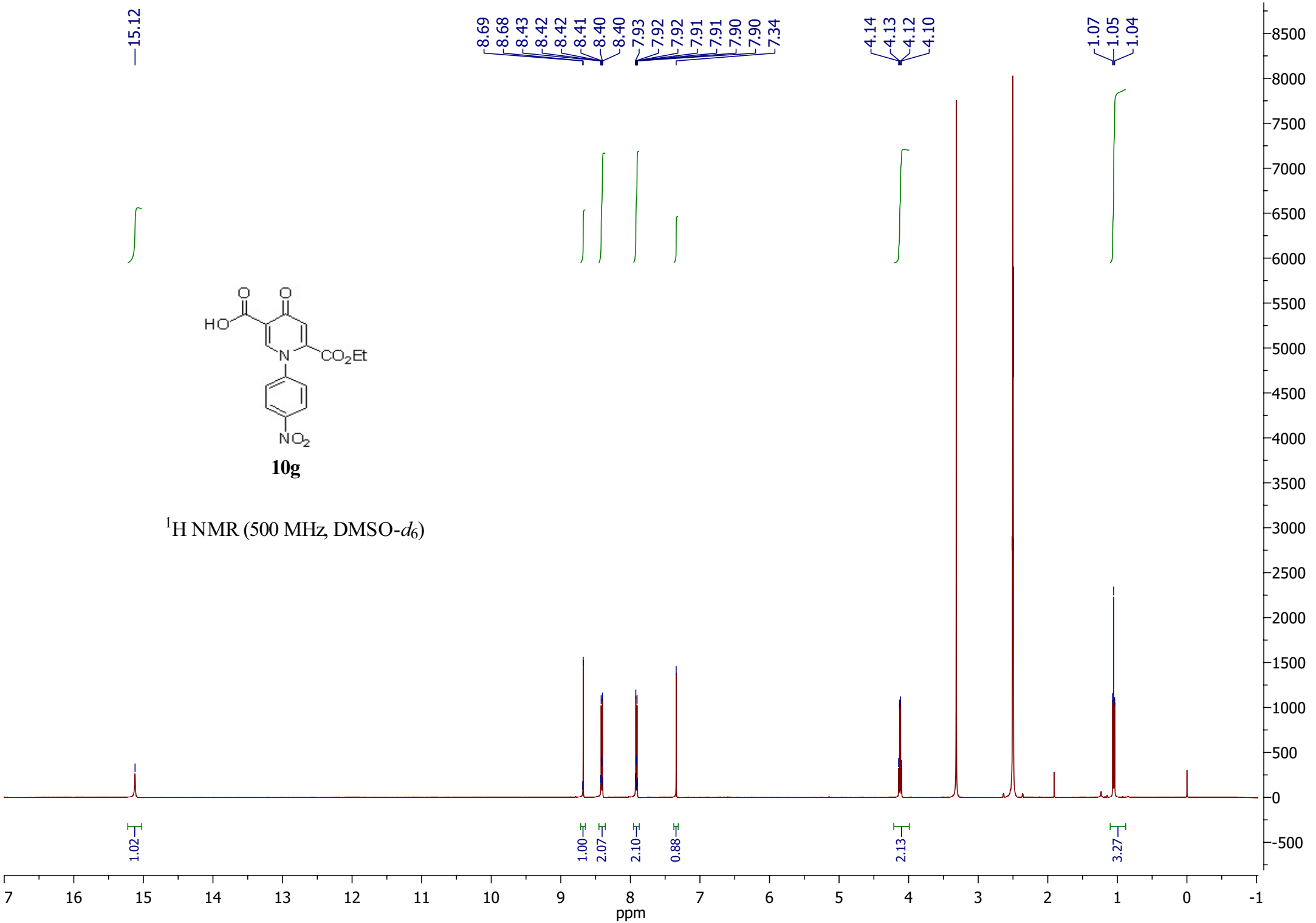
$^1$H NMR (400 MHz, DMSO-$d_6$)




**10f**

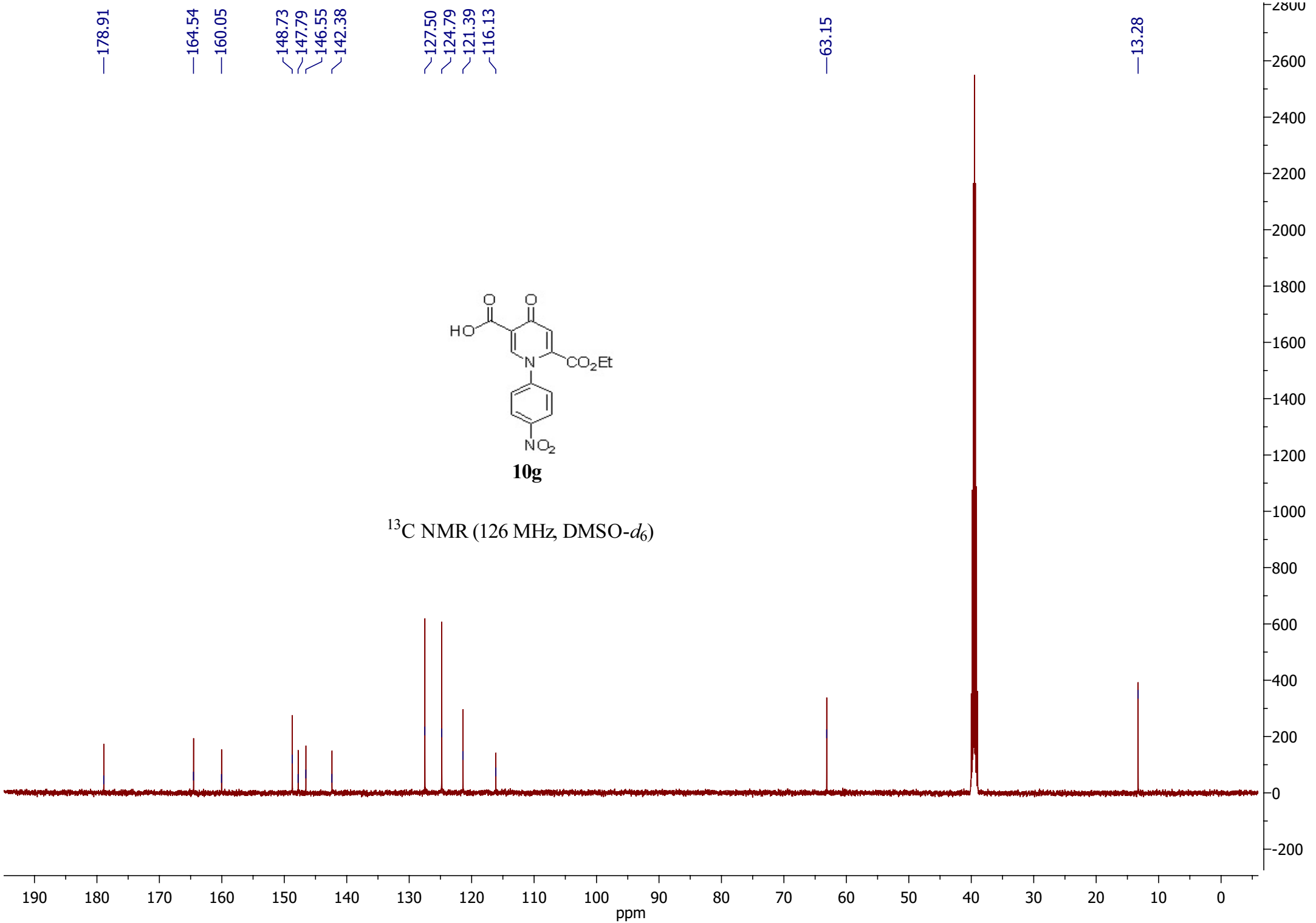
$^{19}$F NMR (376 MHz, DMSO-$d_6$)


178.73
164.61
162.78
160.82
160.15
148.63
143.16
142.68
142.60
131.32
131.25
122.13
122.10
120.65
117.00
116.83
116.01
113.82
113.62
62.94
13.21
HO
O
O
N
CO2Et
F
10f
13C NMR (126 MHz, DMSO-d6)
ppm



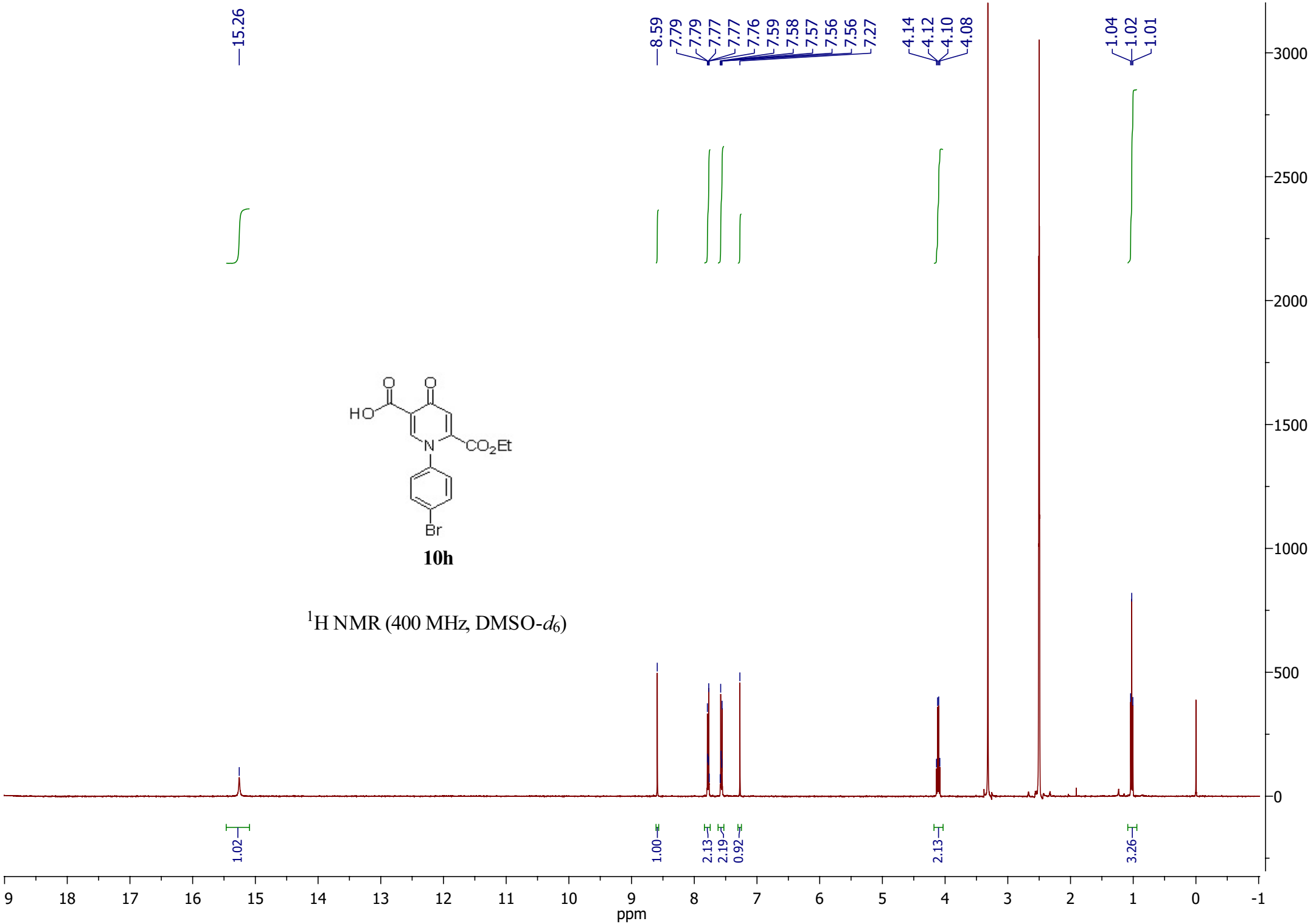

**10g**

$^1$H NMR (500 MHz, DMSO-$d_6$)



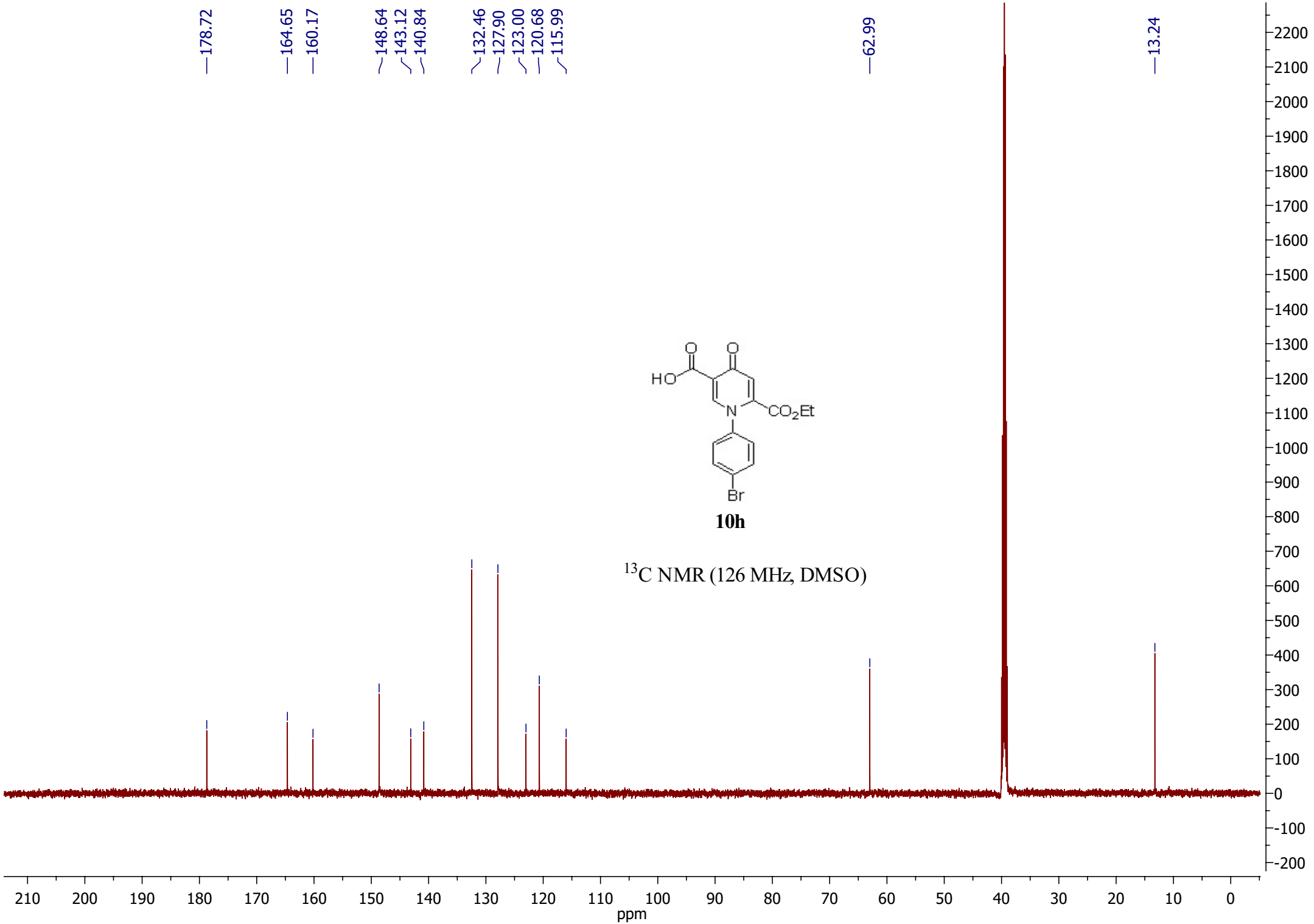

**10g**

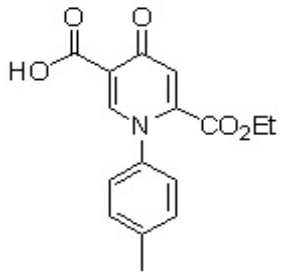
$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**10h**

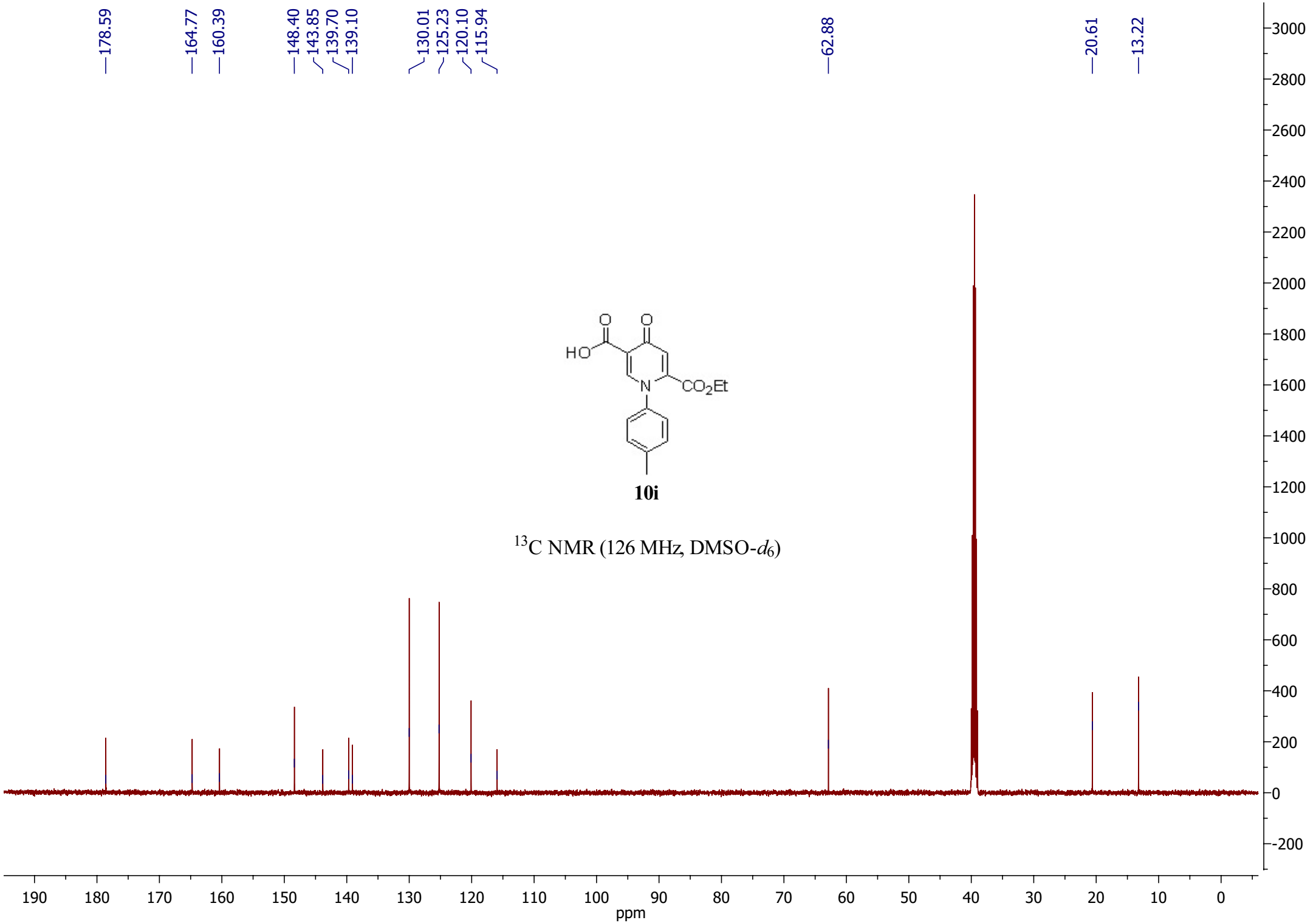
$^1$H NMR (400 MHz, DMSO-$d_6$)

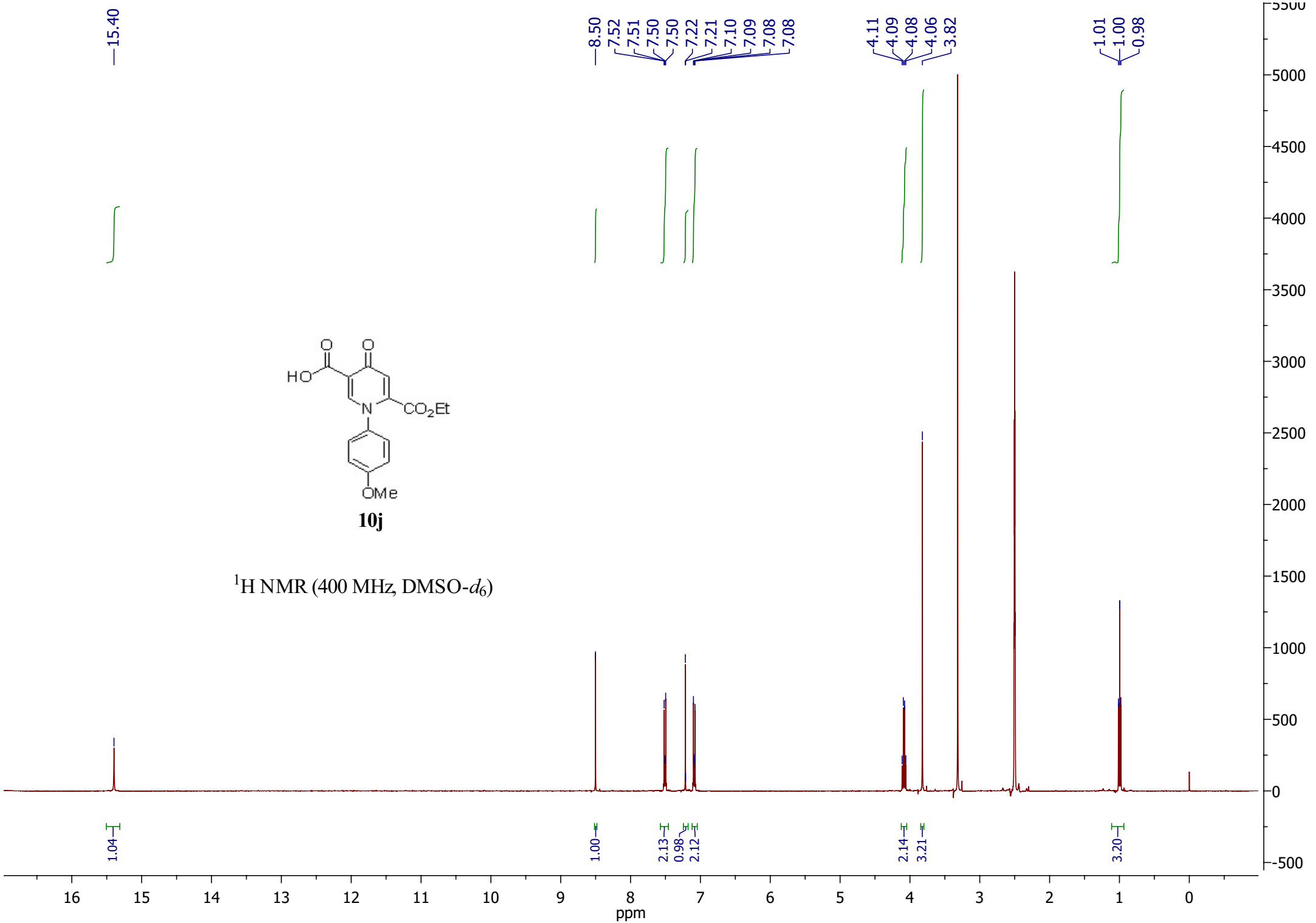

178.72
164.65
160.17
148.64
143.12
140.84
132.46
127.90
123.00
120.68
115.99
62.99
13.24
HO
O
O
N
CO2Et
Br
10h
13C NMR (126 MHz, DMSO)
ppm



**10i**

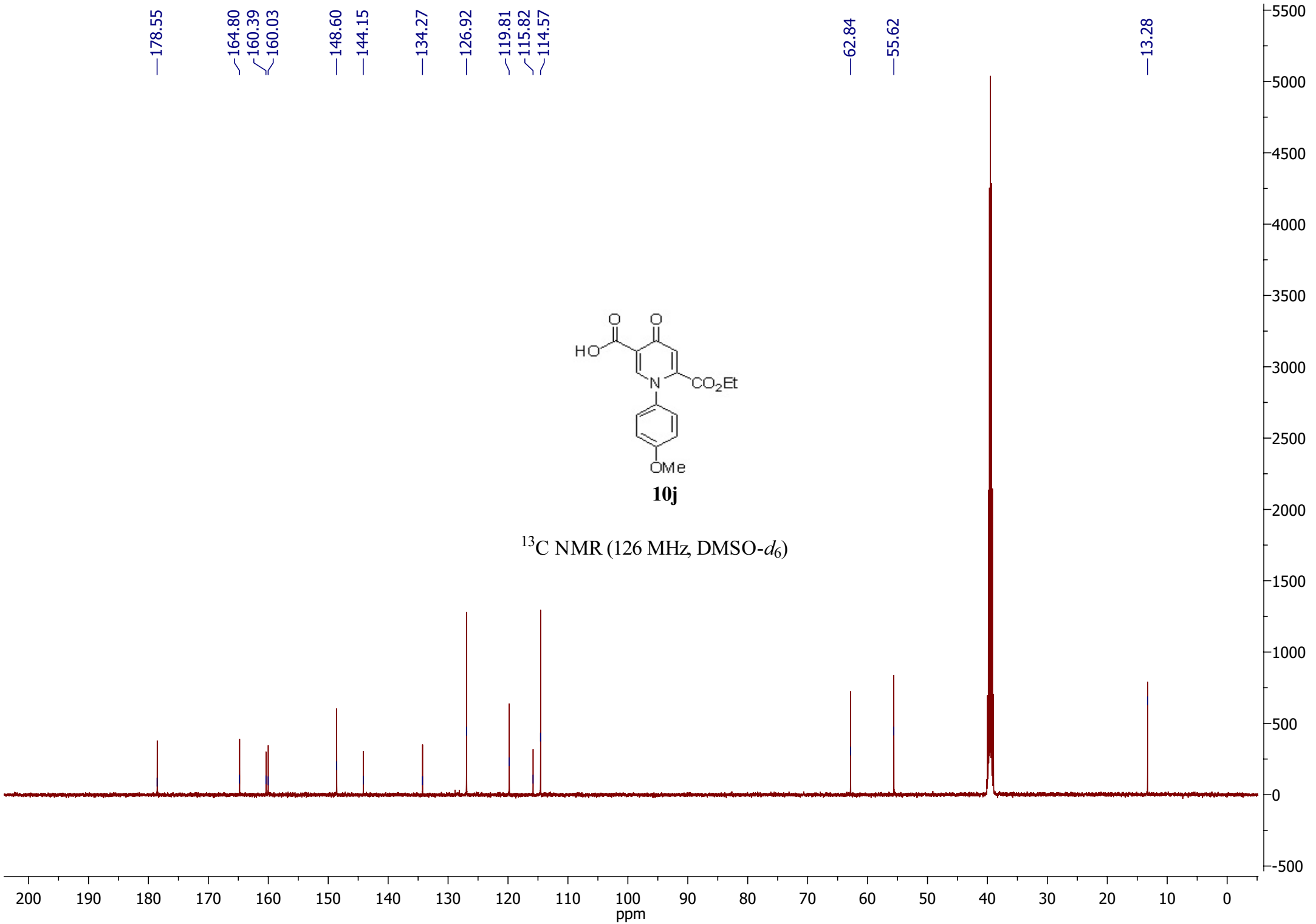
$^1$H NMR (500 MHz, DMSO-$d_6$)


178.59
164.77
160.39
148.40
143.85
139.70
139.10
130.01
125.23
120.10
115.94
62.88
20.61
13.22
HO
O
O
N
CO2Et
10i
13C NMR (126 MHz, DMSO-d6)
ppm



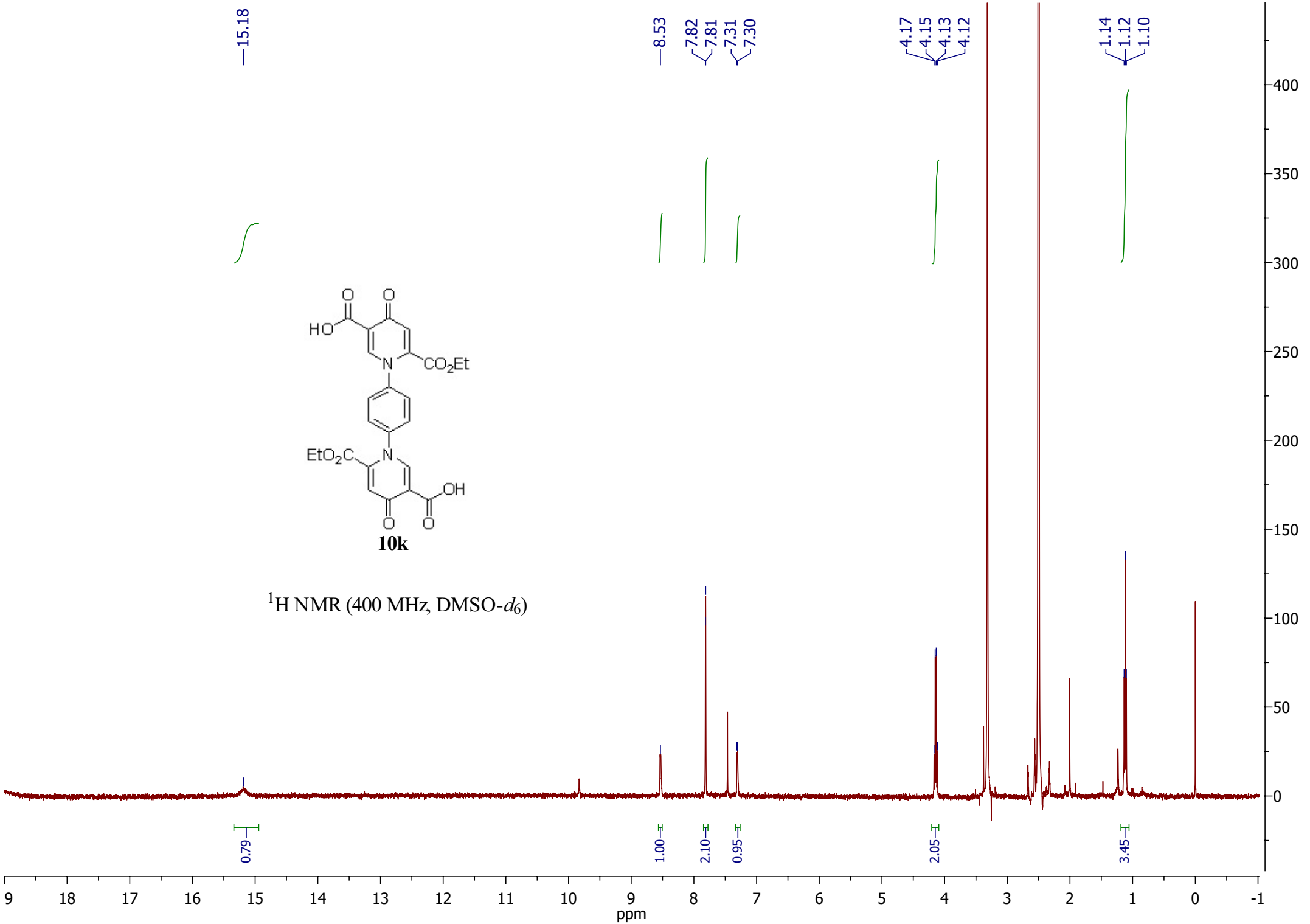

**10j**

$^1$H NMR (400 MHz, DMSO-$d_6$)



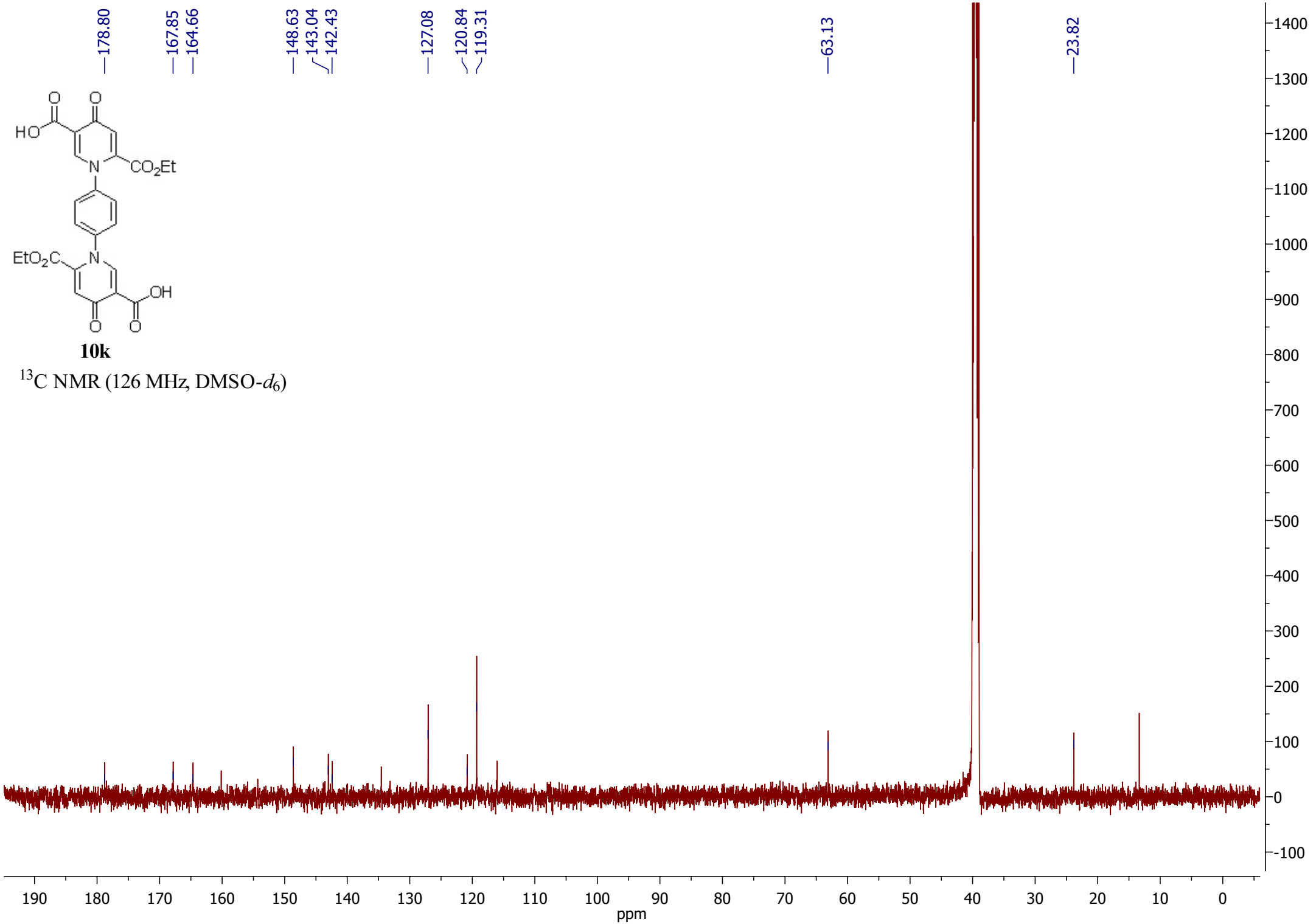

**10j**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



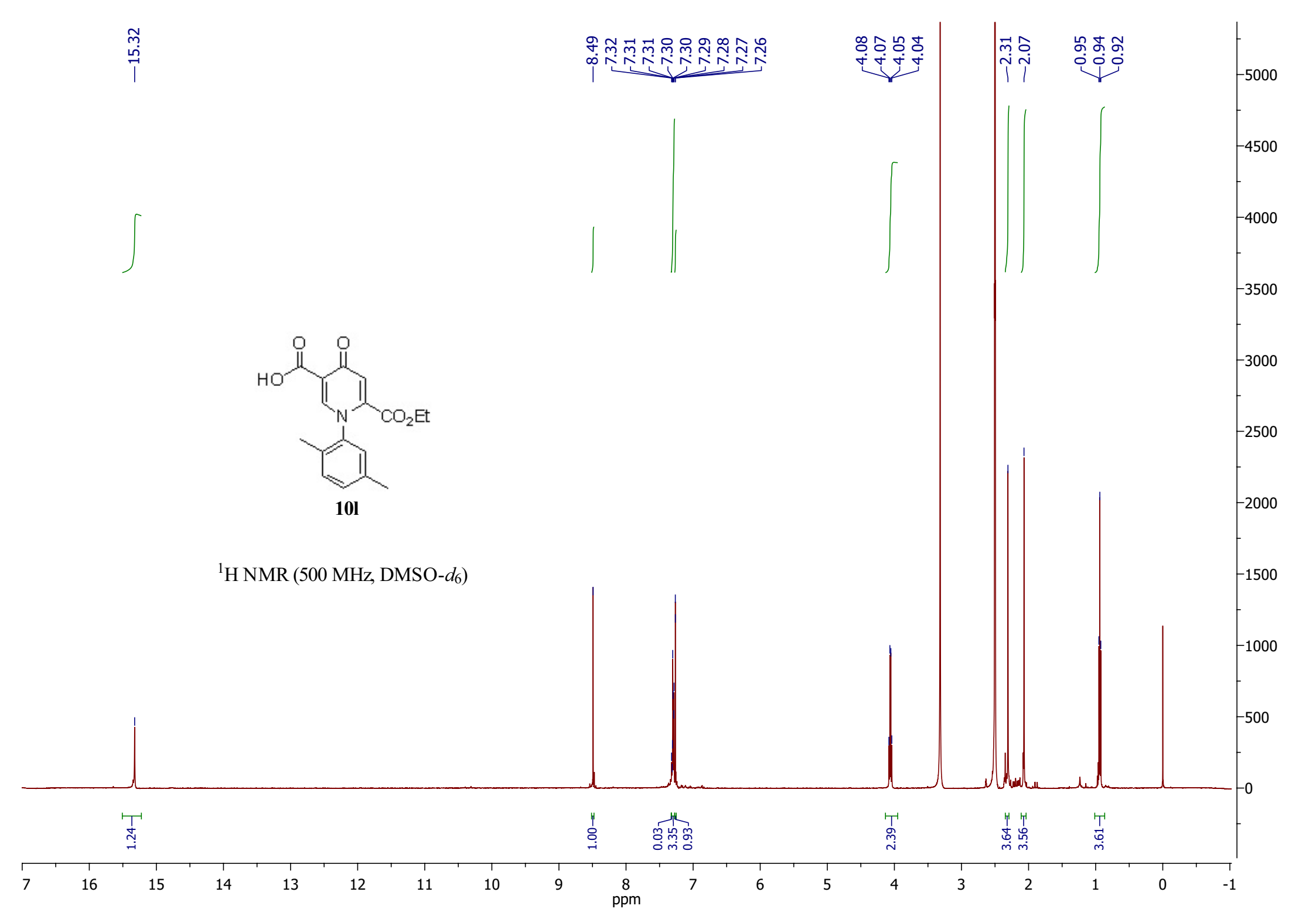

**10k**

$^1$H NMR (400 MHz, DMSO-$d_6$)



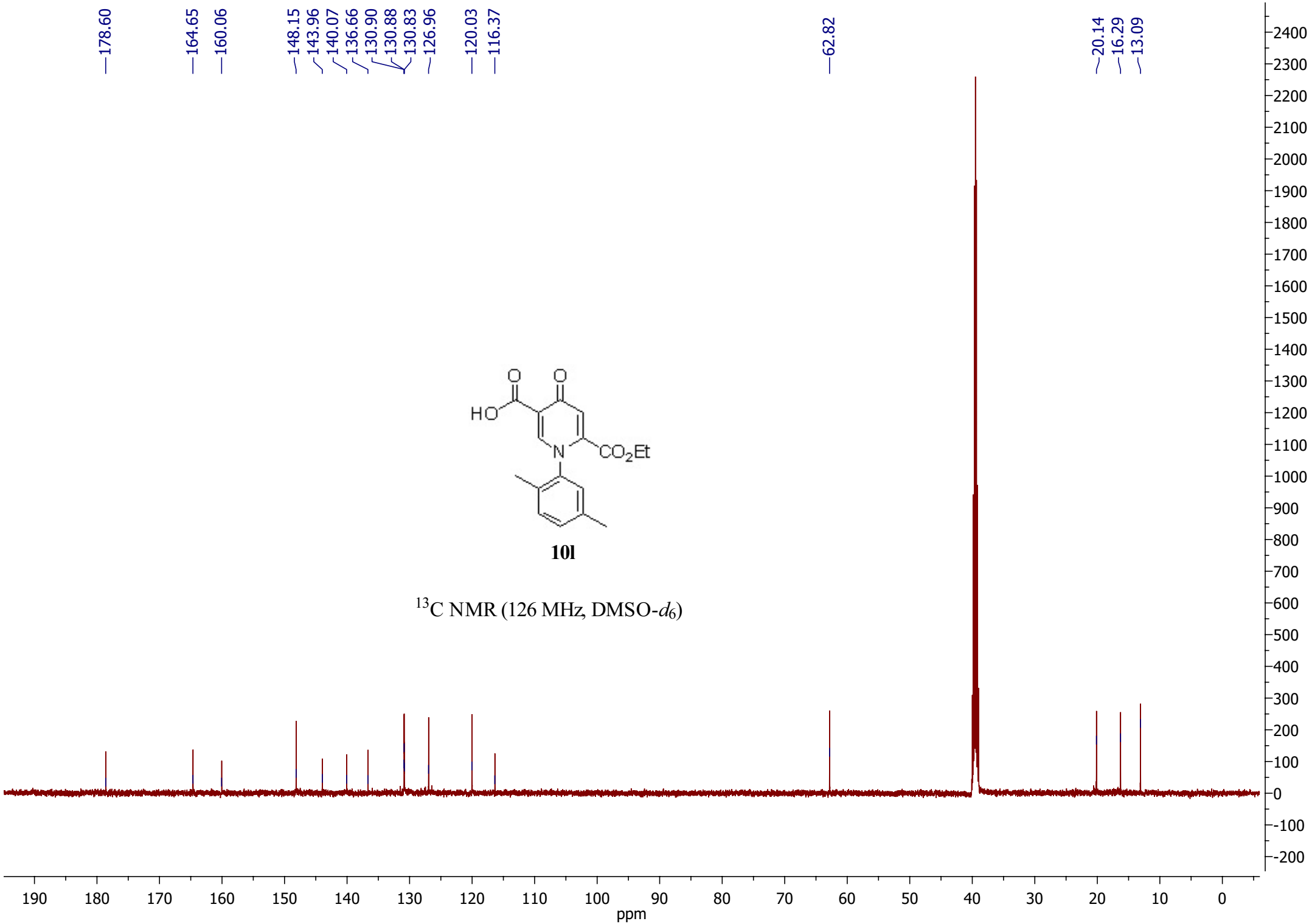

**10k**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



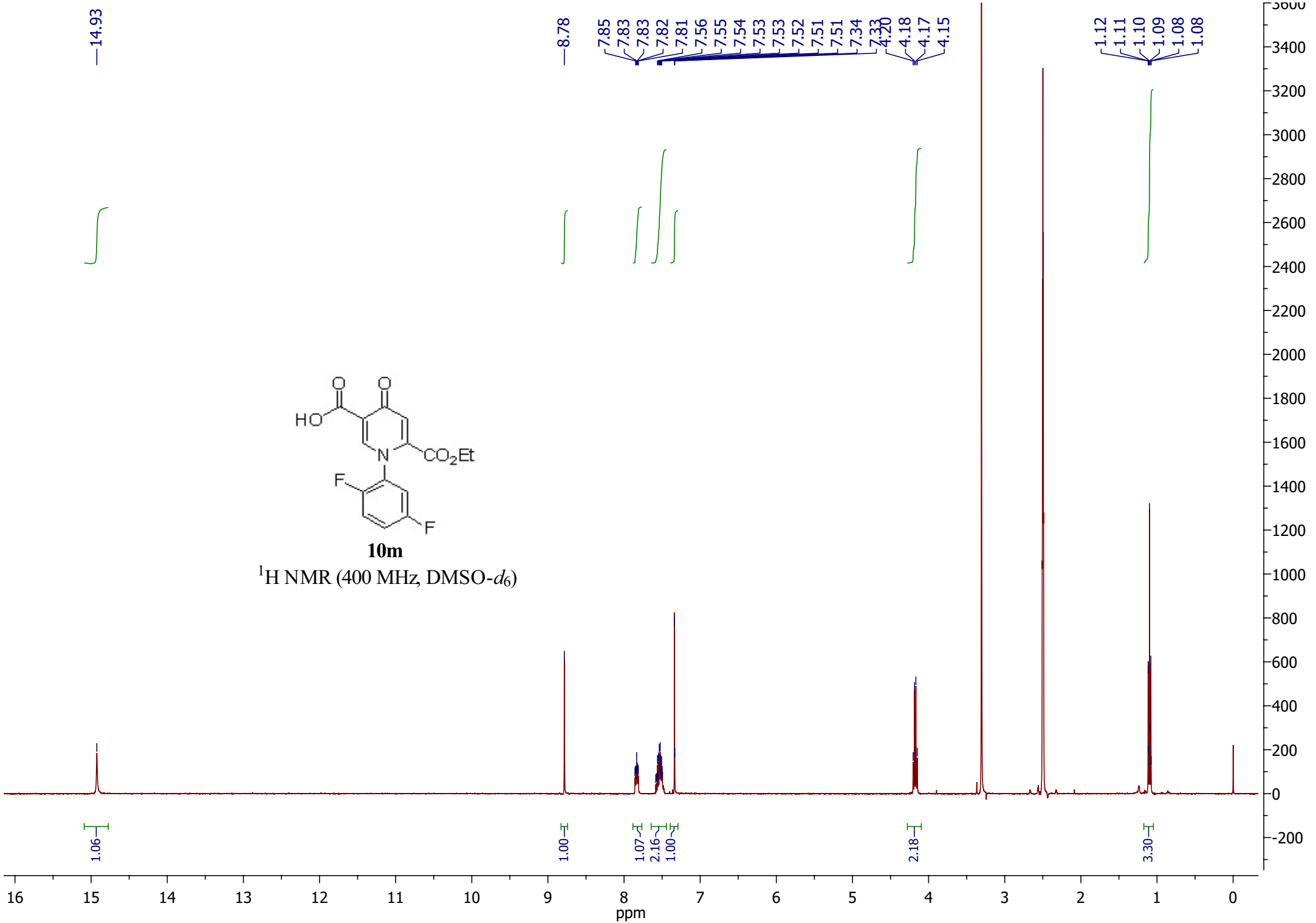

**10l**

$^1$H NMR (500 MHz, DMSO-$d_6$)



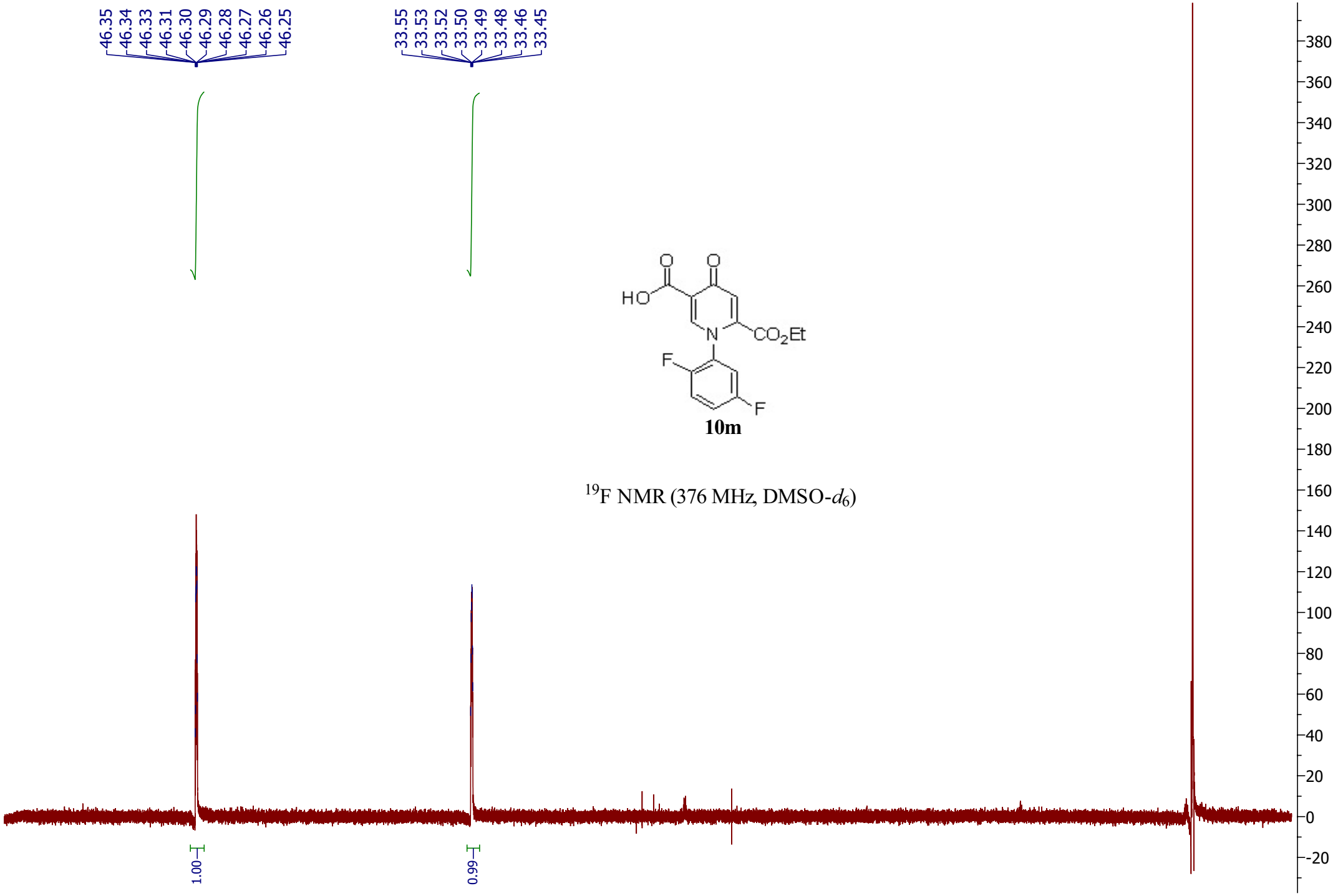

**10l**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



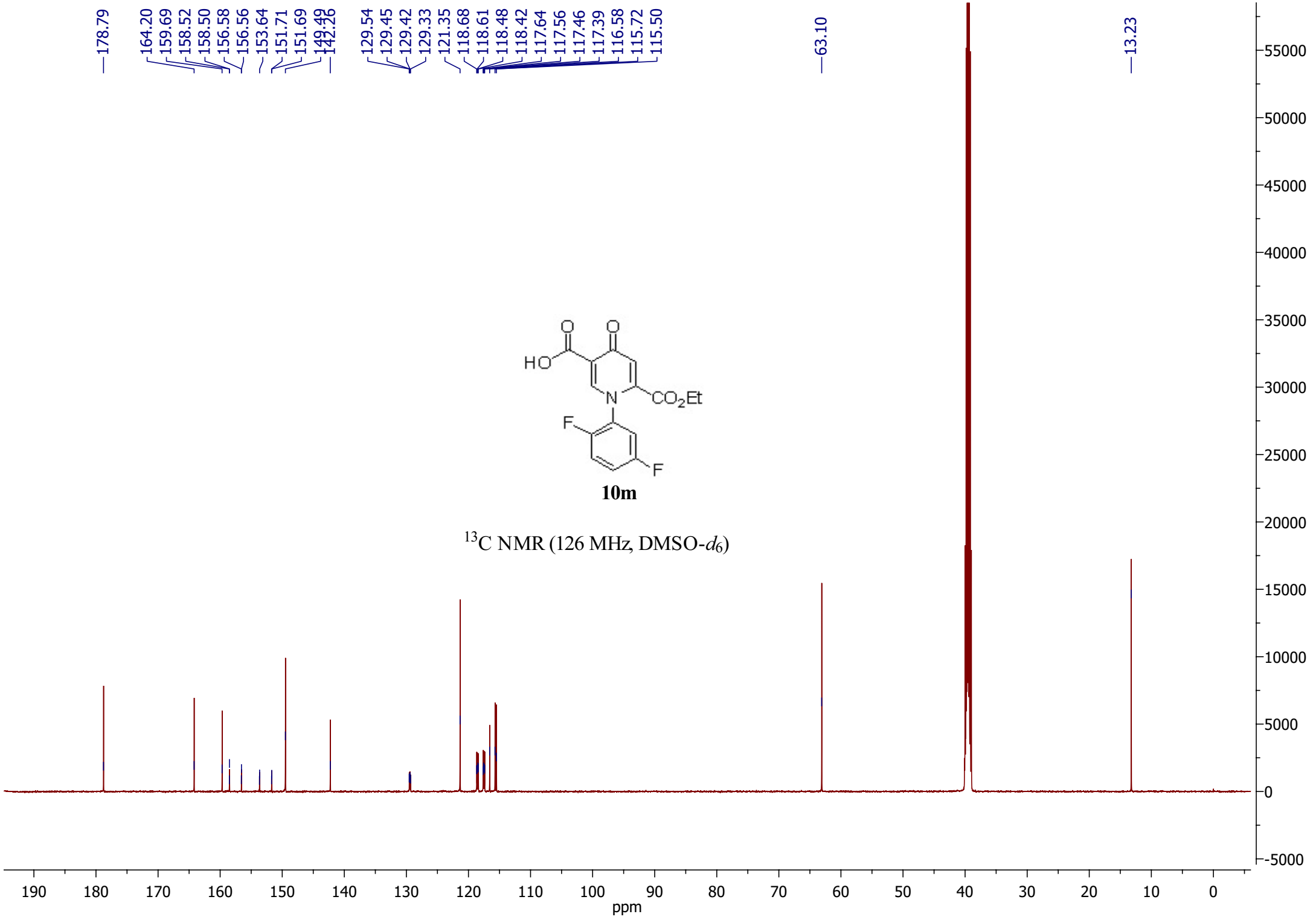

**10m**

$^1$H NMR (400 MHz, DMSO-$d_6$)



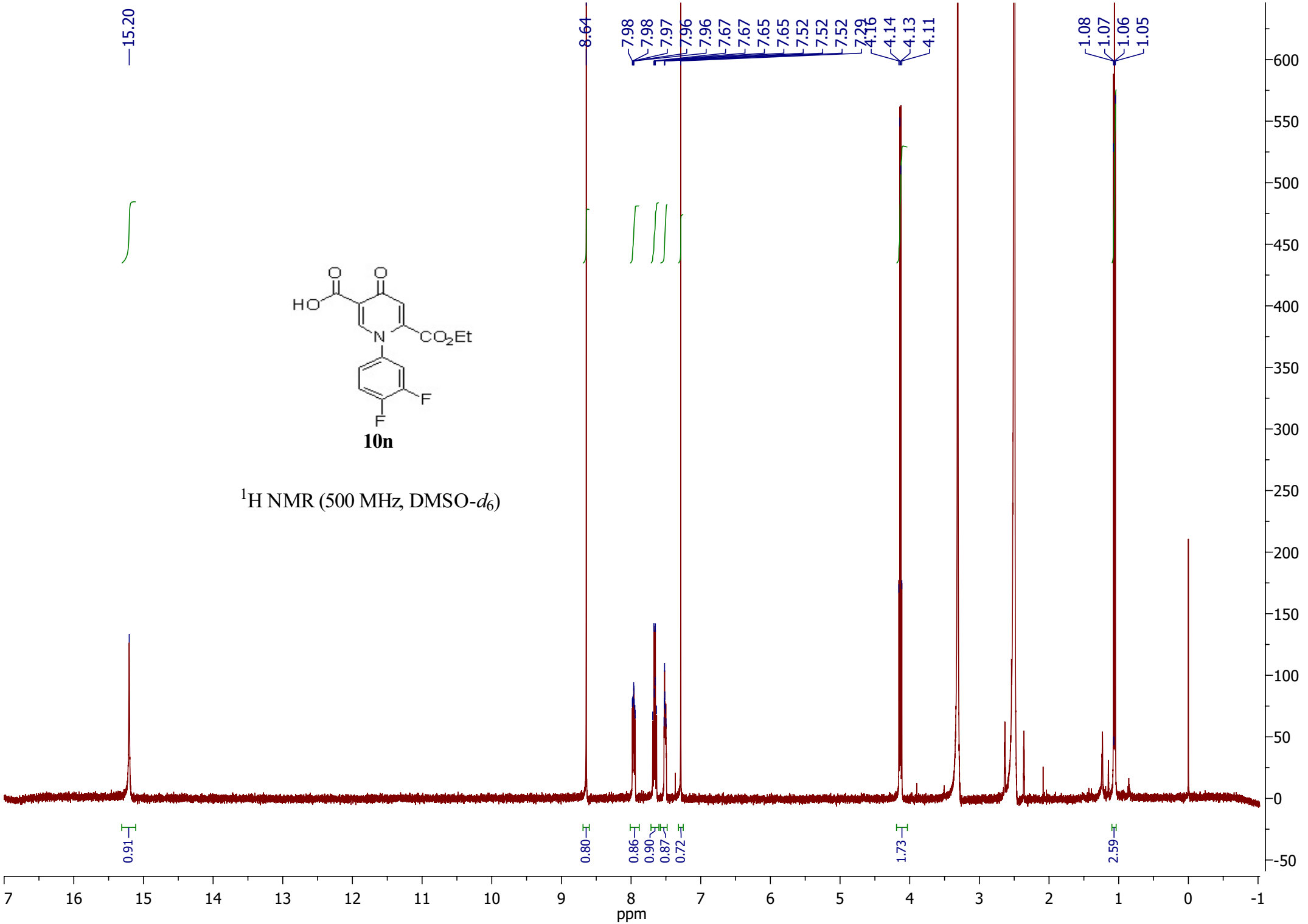

**10m**

$^{19}$F NMR (376 MHz, DMSO-$d_6$)



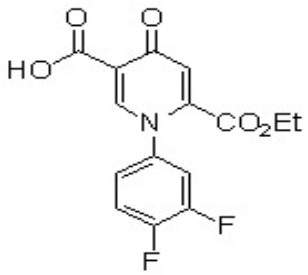

**10m**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



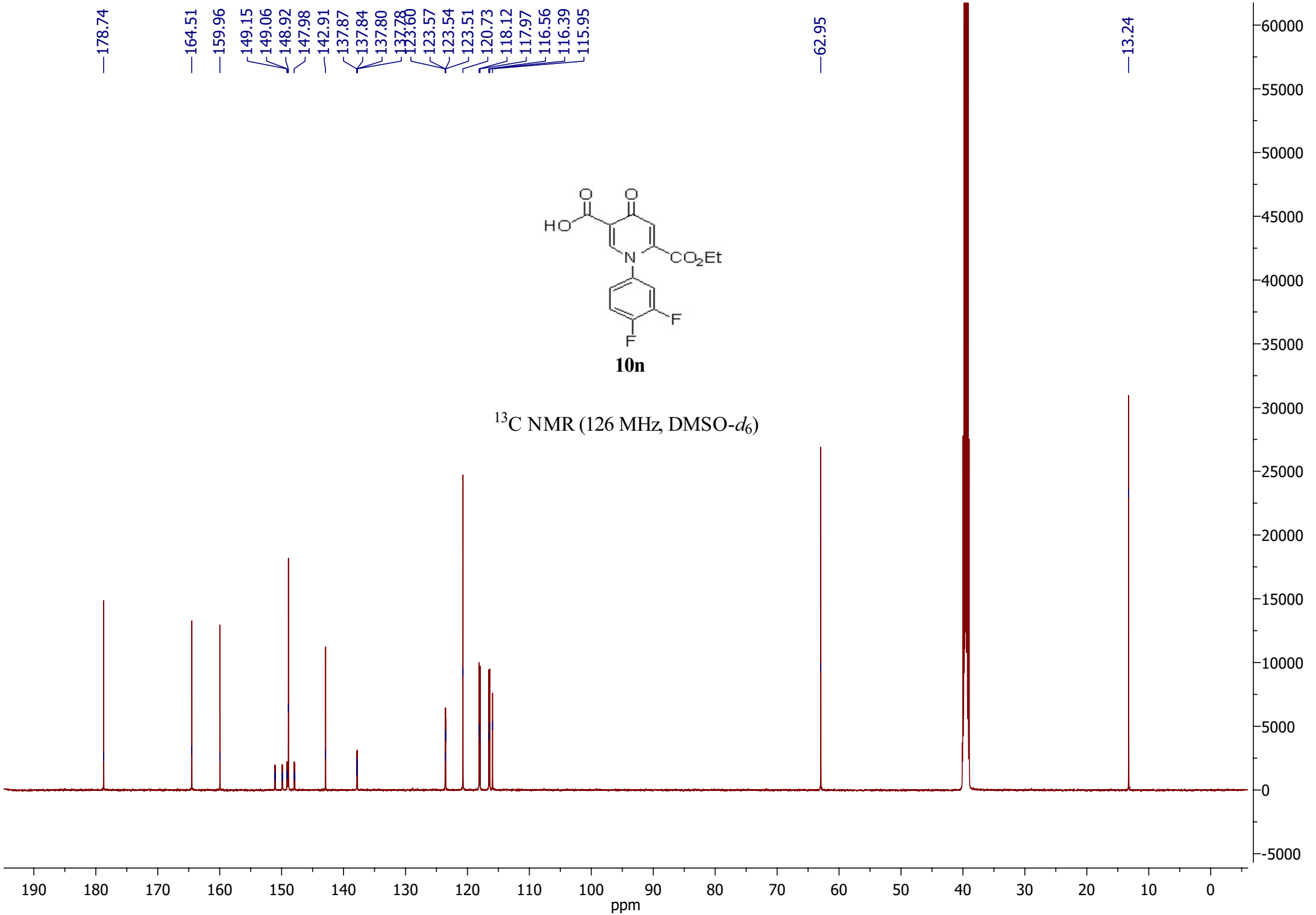

**10n**

$^1$H NMR (500 MHz, DMSO-$d_6$)



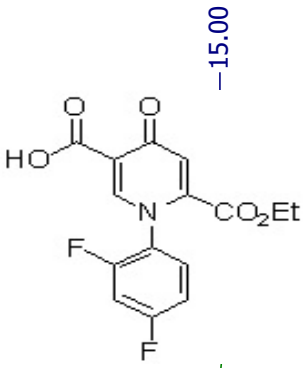

**10n**

$^{19}$F NMR (471 MHz, DMSO-$d_6$)



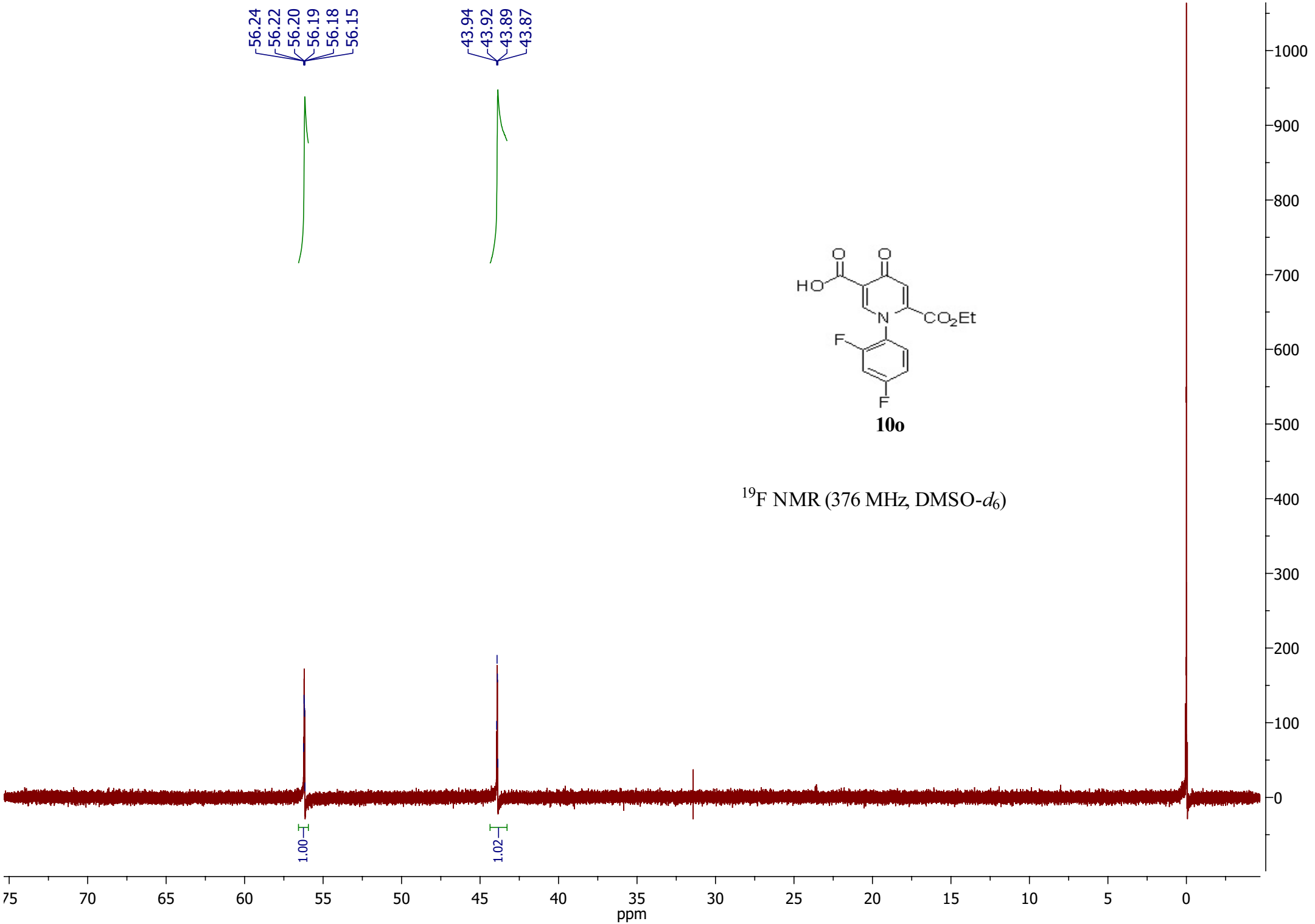

**10n**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



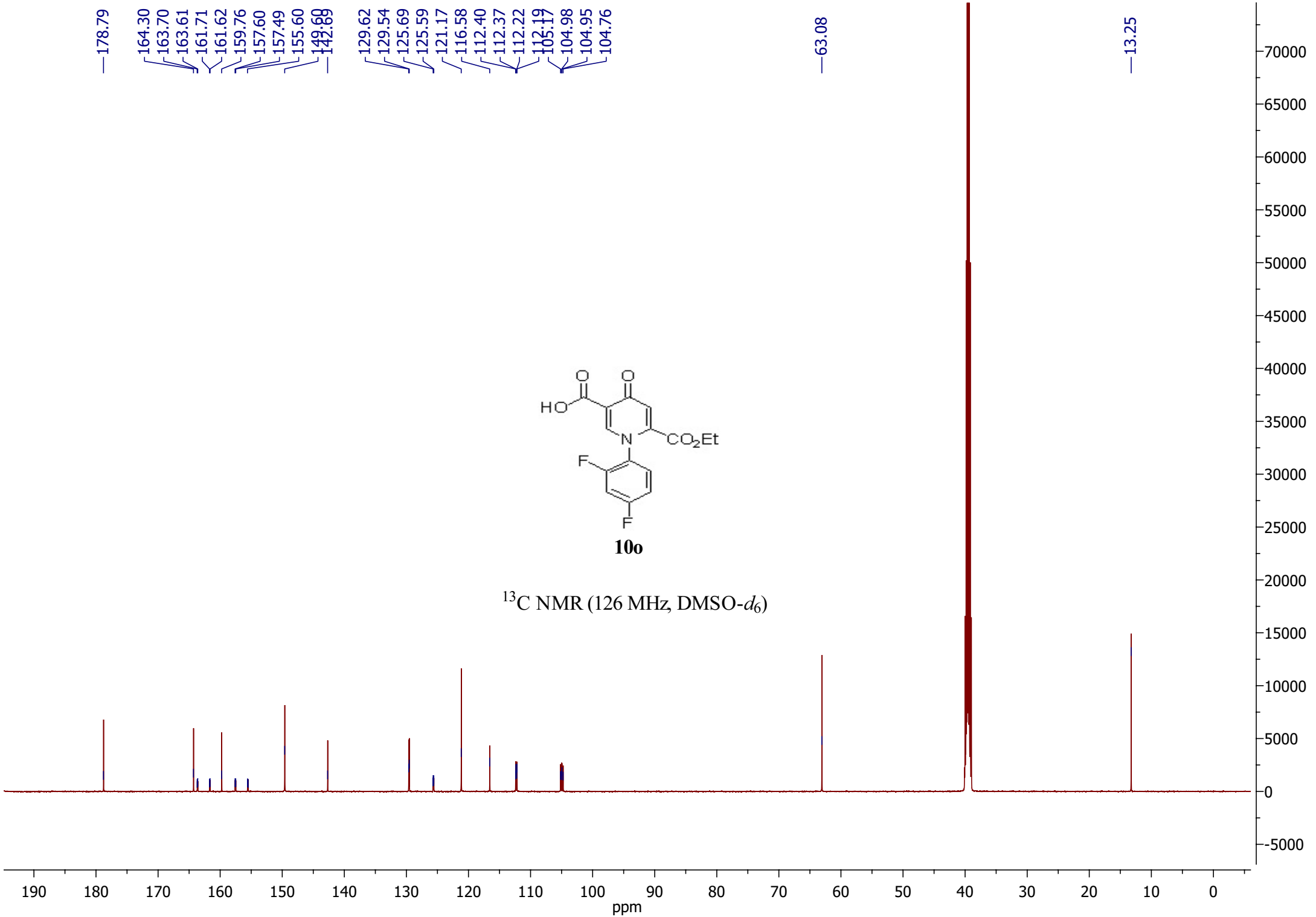

**10o**

$^1$H NMR (400 MHz, DMSO-$d_6$)



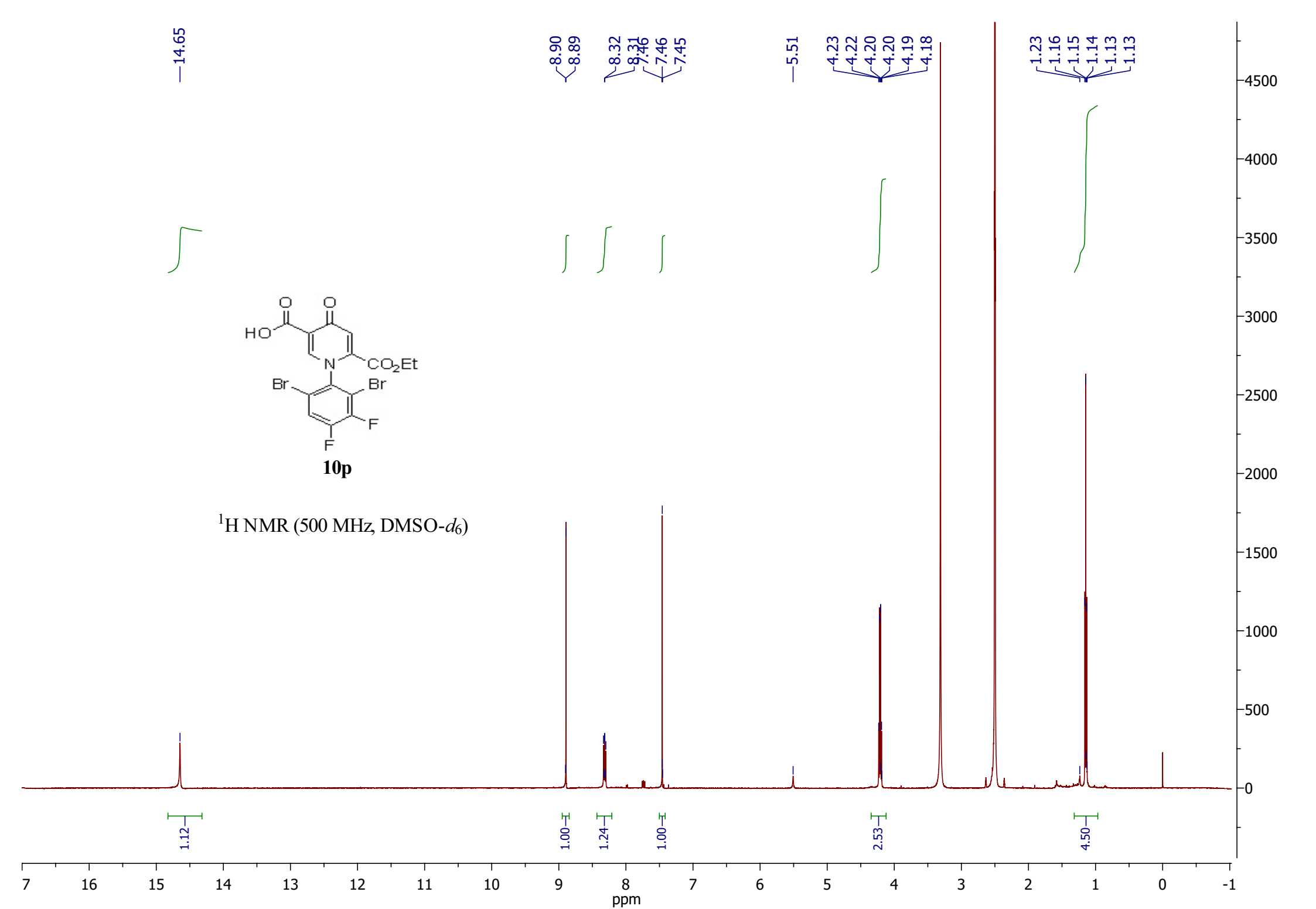

**10o**

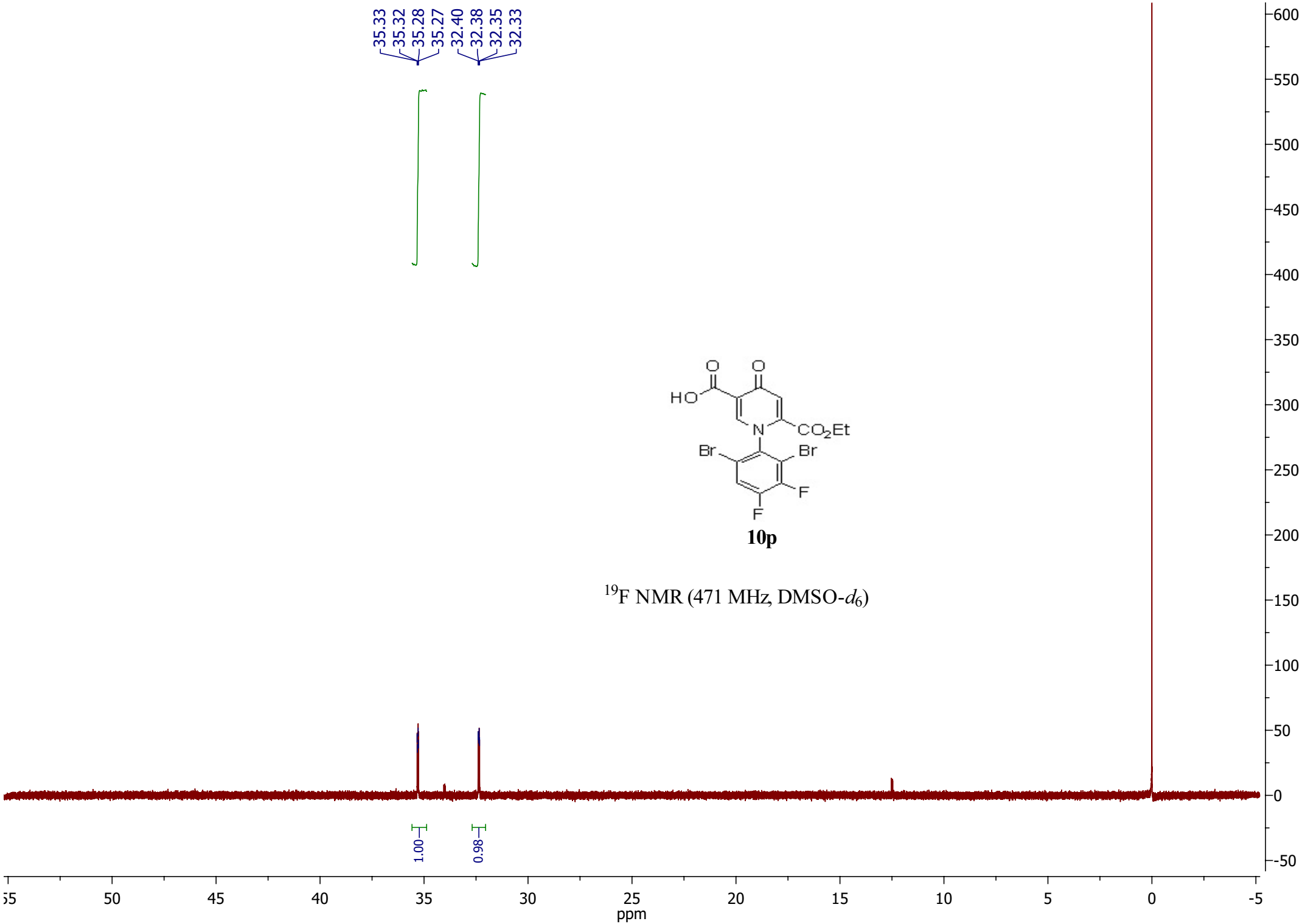
$^{19}$F NMR (376 MHz, DMSO-$d_6$)




**10o**

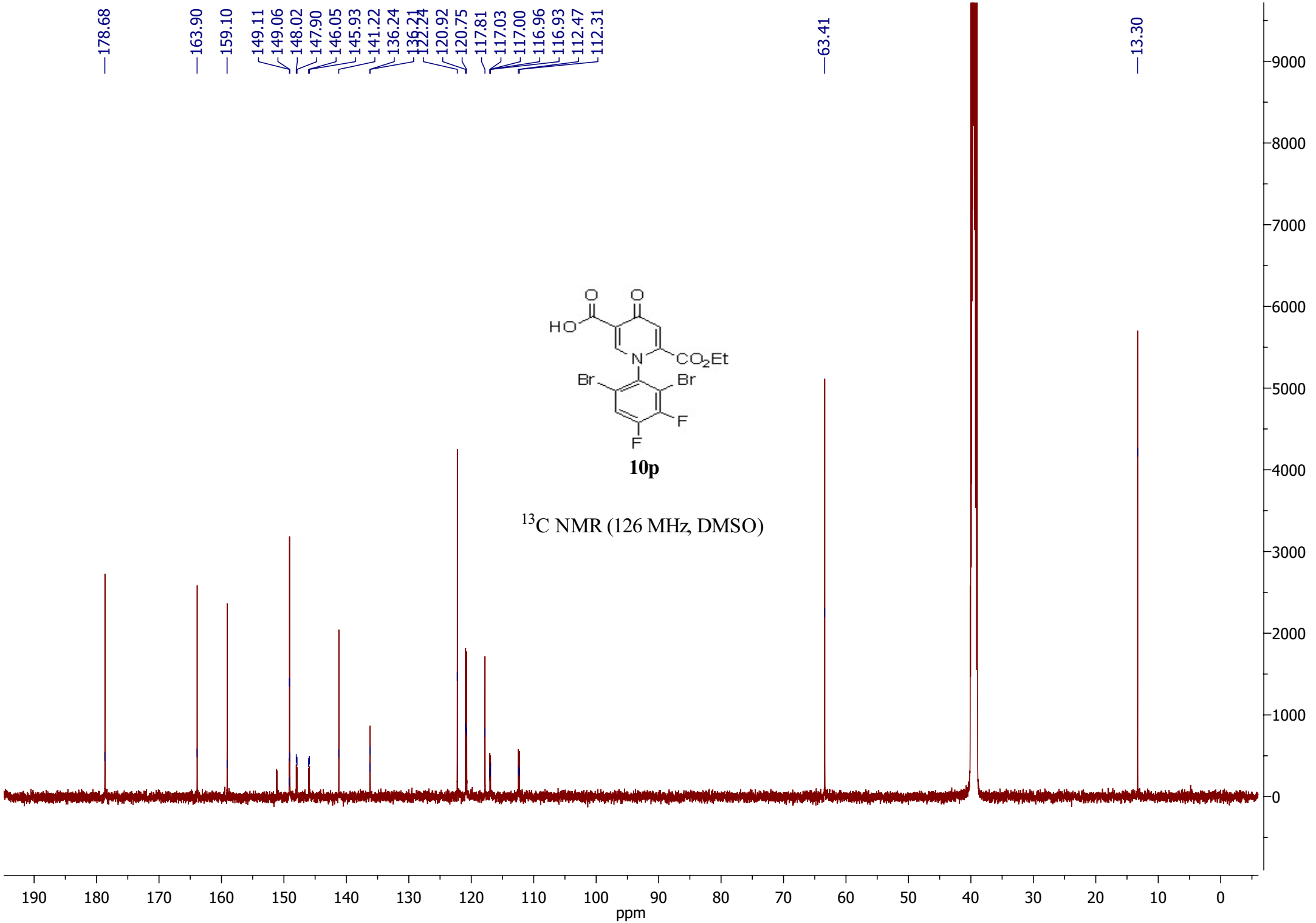
$^{13}$C NMR (126 MHz, DMSO-$d_6$)


14.65
8.90
8.89
8.32
8.31
7.46
7.45
5.51
4.23
4.22
4.20
4.20
4.19
4.18
1.23
1.16
1.15
1.14
1.13
1.13
HO
O
O
N
CO2Et
Br
Br
F
F
10p
1H NMR (500 MHz, DMSO-d6)
1.12
1.00
1.24
1.00
2.53
4.50
ppm



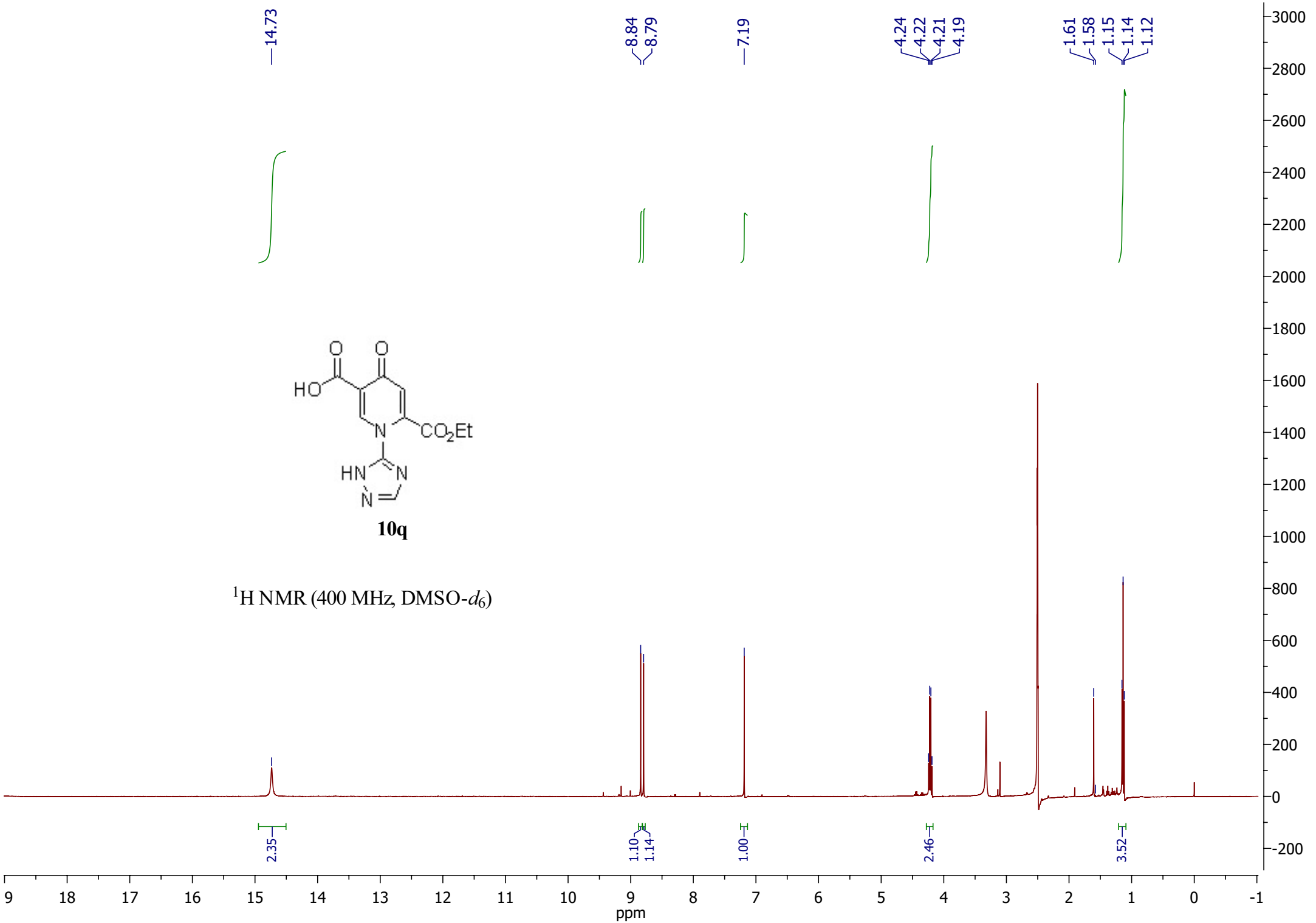

**10p**

$^{19}$F NMR (471 MHz, DMSO-$d_6$)



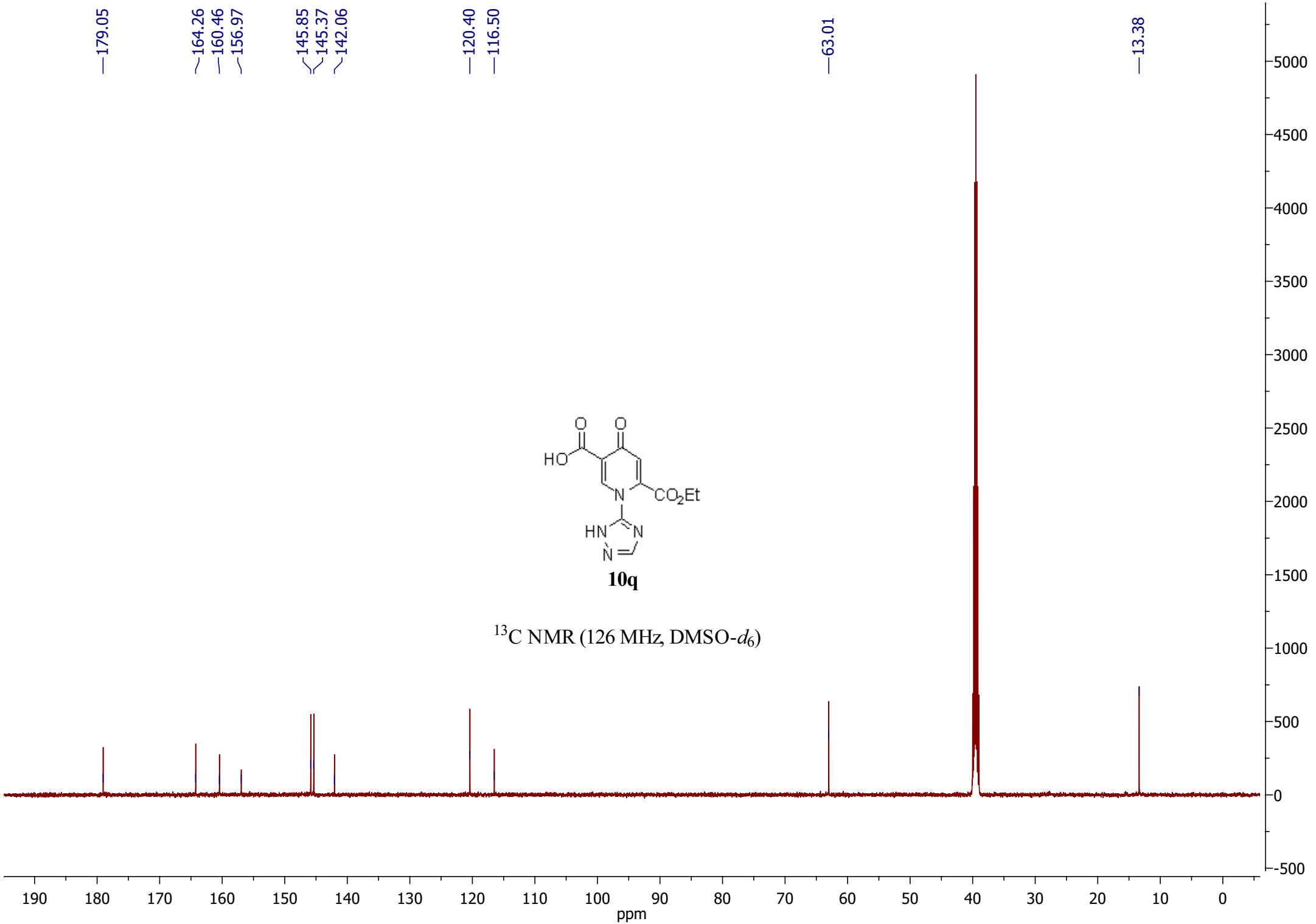

**10p**

$^{13}$C NMR (126 MHz, DMSO)



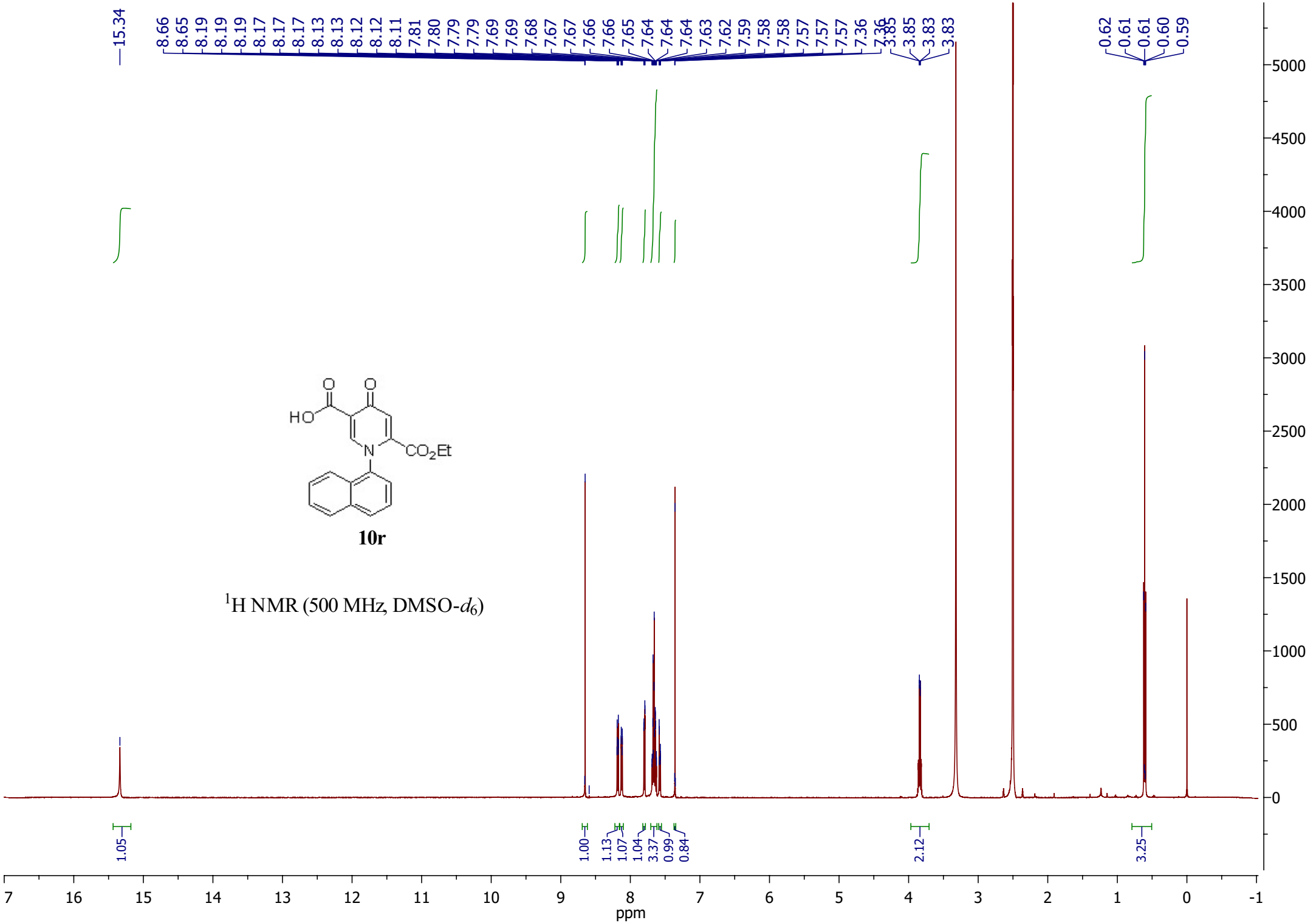

**10q**

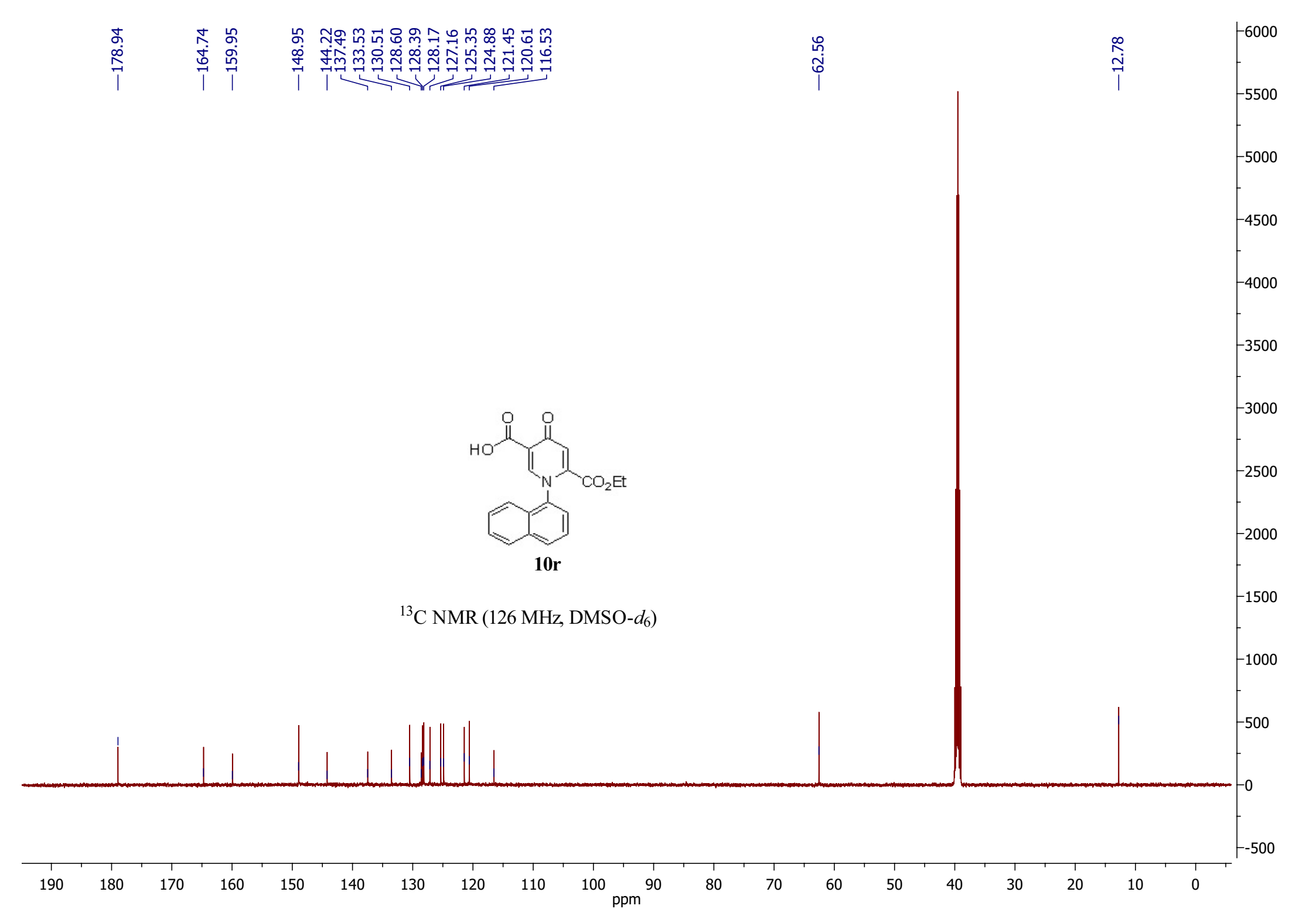
$^1$H NMR (400 MHz, DMSO-$d_6$)

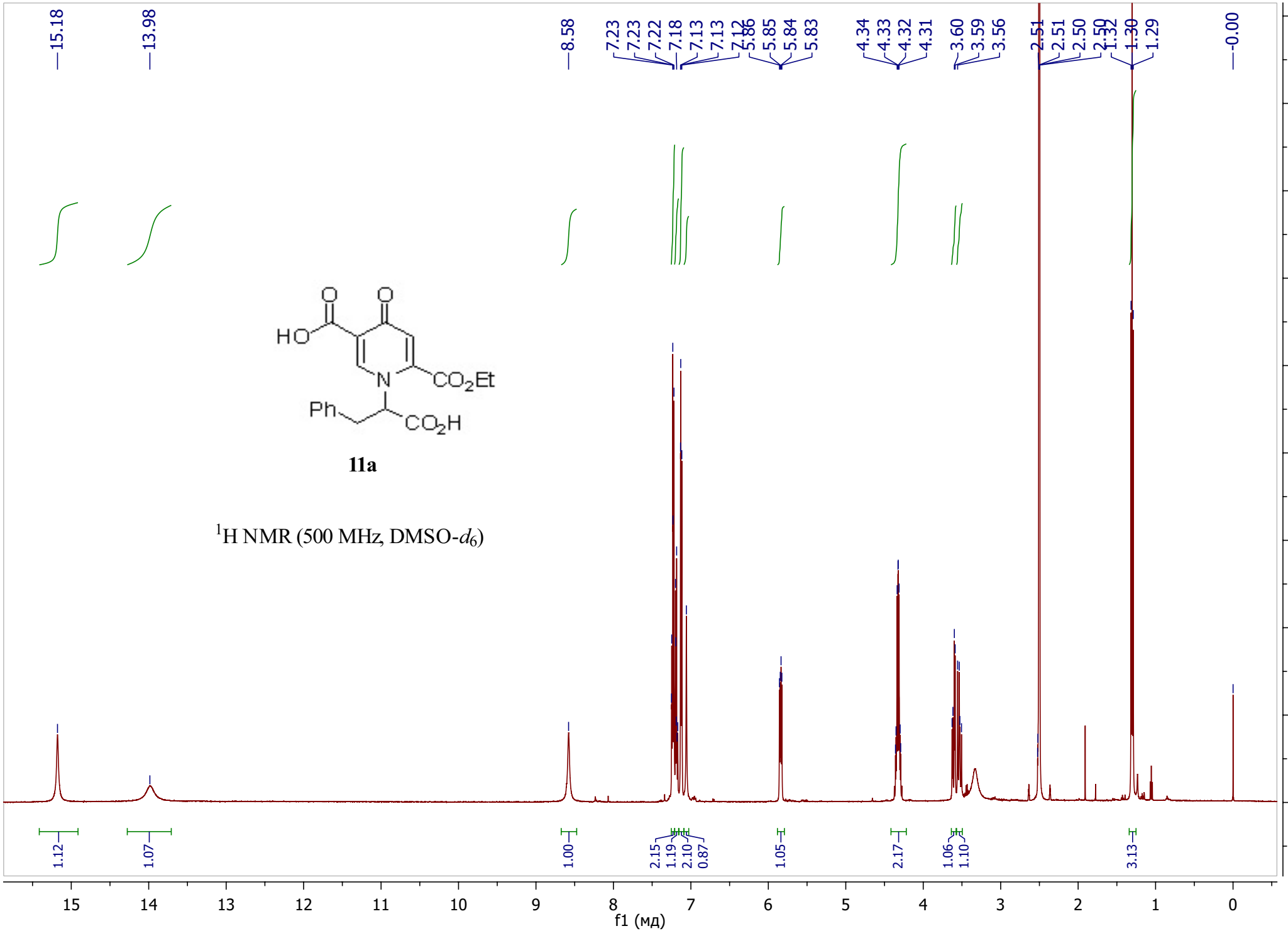



**10q**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)

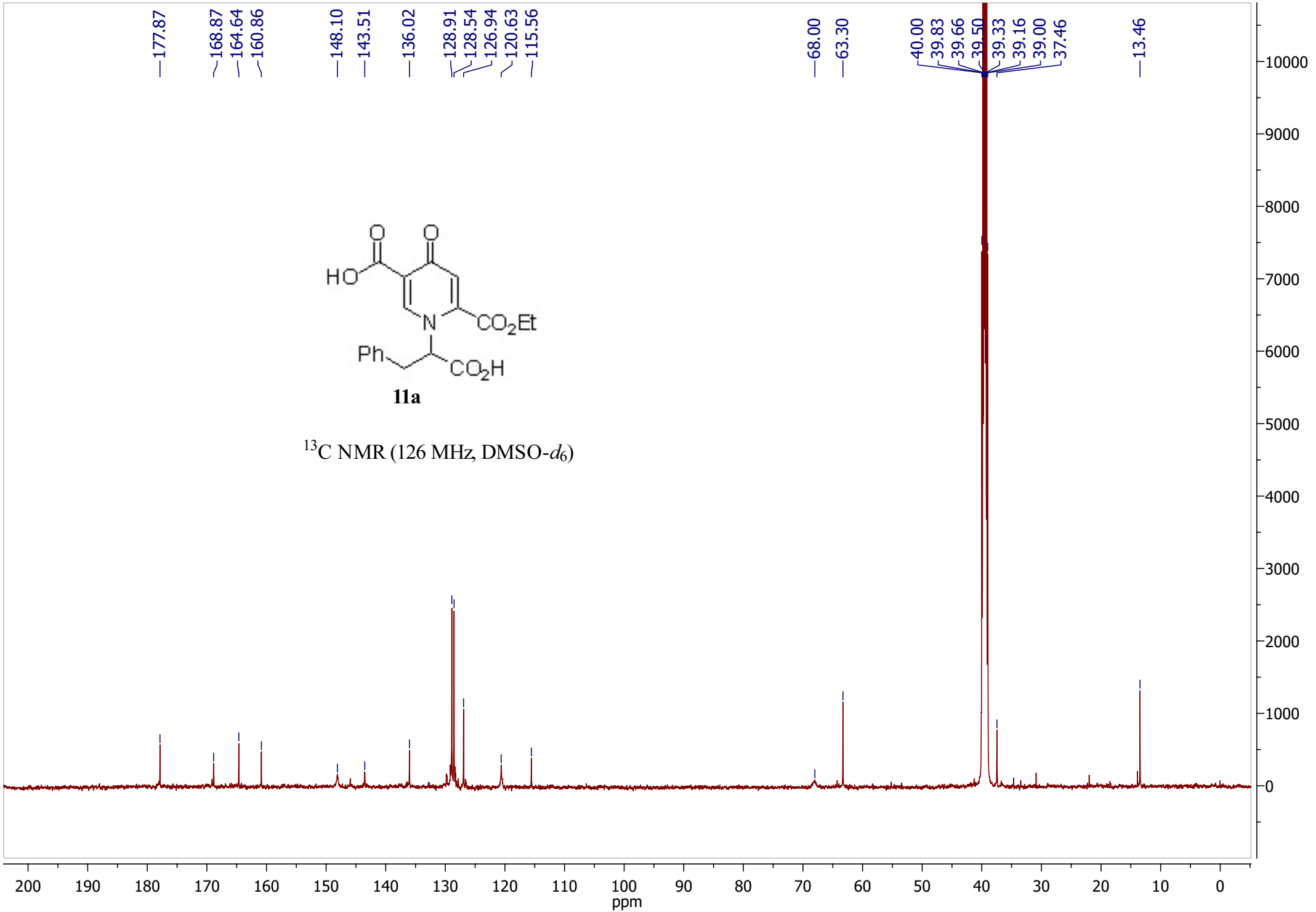

15.34
8.66 8.65 8.19 8.19 8.19 8.17 8.17 8.17 8.13 8.13 8.12 8.12 8.11 7.81 7.80 7.79 7.79 7.69 7.69 7.68 7.67 7.67 7.66 7.66 7.65 7.64 7.64 7.64 7.63 7.62 7.59 7.58 7.58 7.57 7.57 7.57 7.36 7.36 3.85 3.85 3.83 3.83
0.62 0.61 0.61 0.60 0.59
HO
O
O
N
CO2Et
10r
1H NMR (500 MHz, DMSO-d6)
1.05 1.00 1.13 1.07 1.04 3.37 0.99 0.84 2.12 3.25
ppm


178.94
164.74
159.95
148.95
144.22
137.49
133.53
130.51
128.60
128.39
128.17
127.16
125.35
124.88
121.45
120.61
116.53
62.56
12.78
HO
O
O
N
CO2Et
10r
13C NMR (126 MHz, DMSO-d6)
ppm



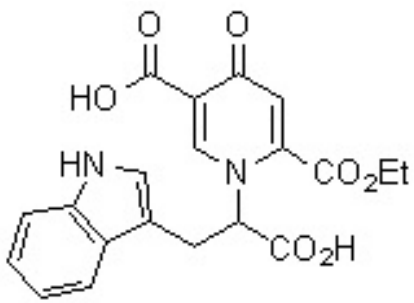

**11a**

$^{1}$H NMR (500 MHz, DMSO-$d_6$)



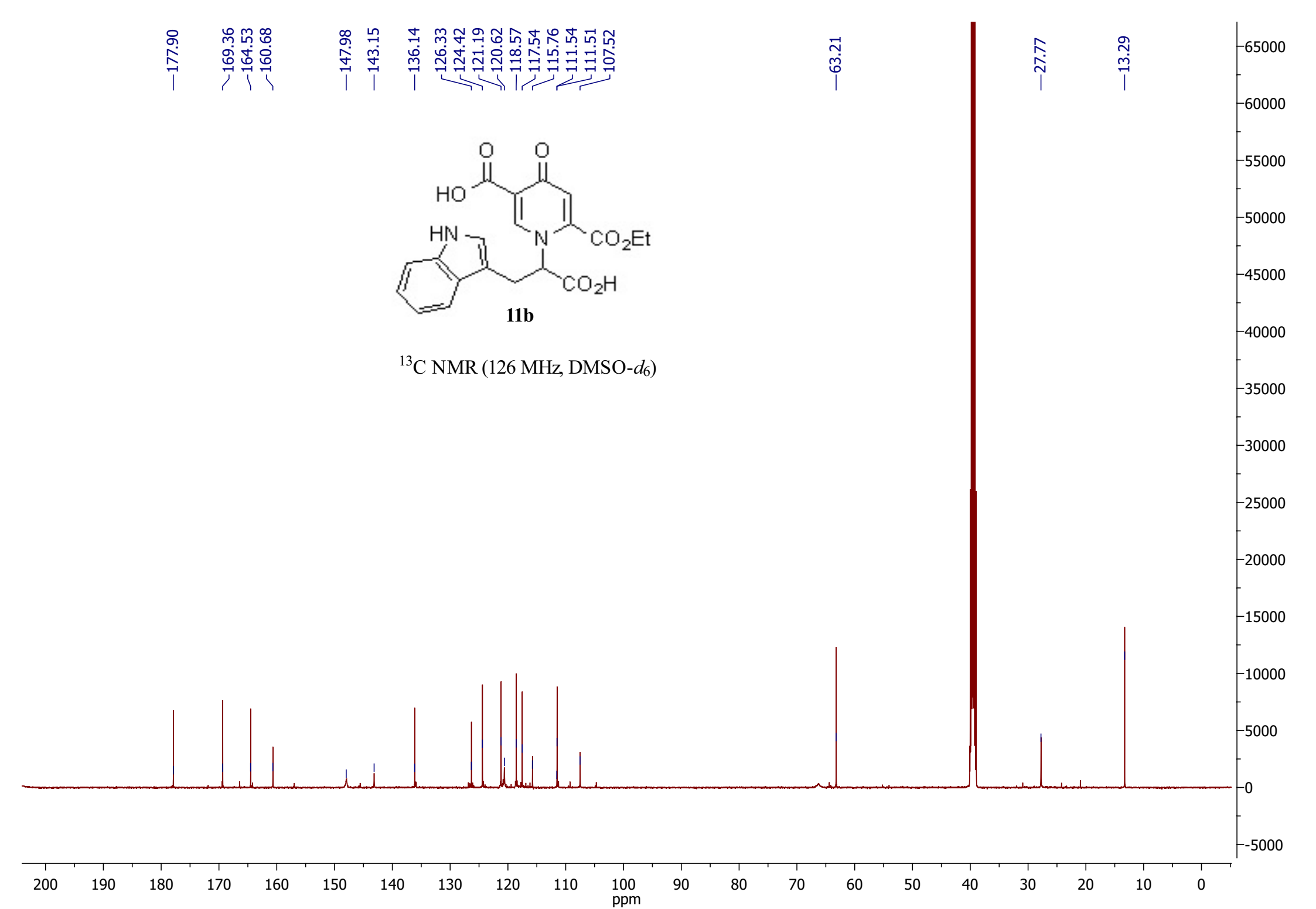

**11a**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



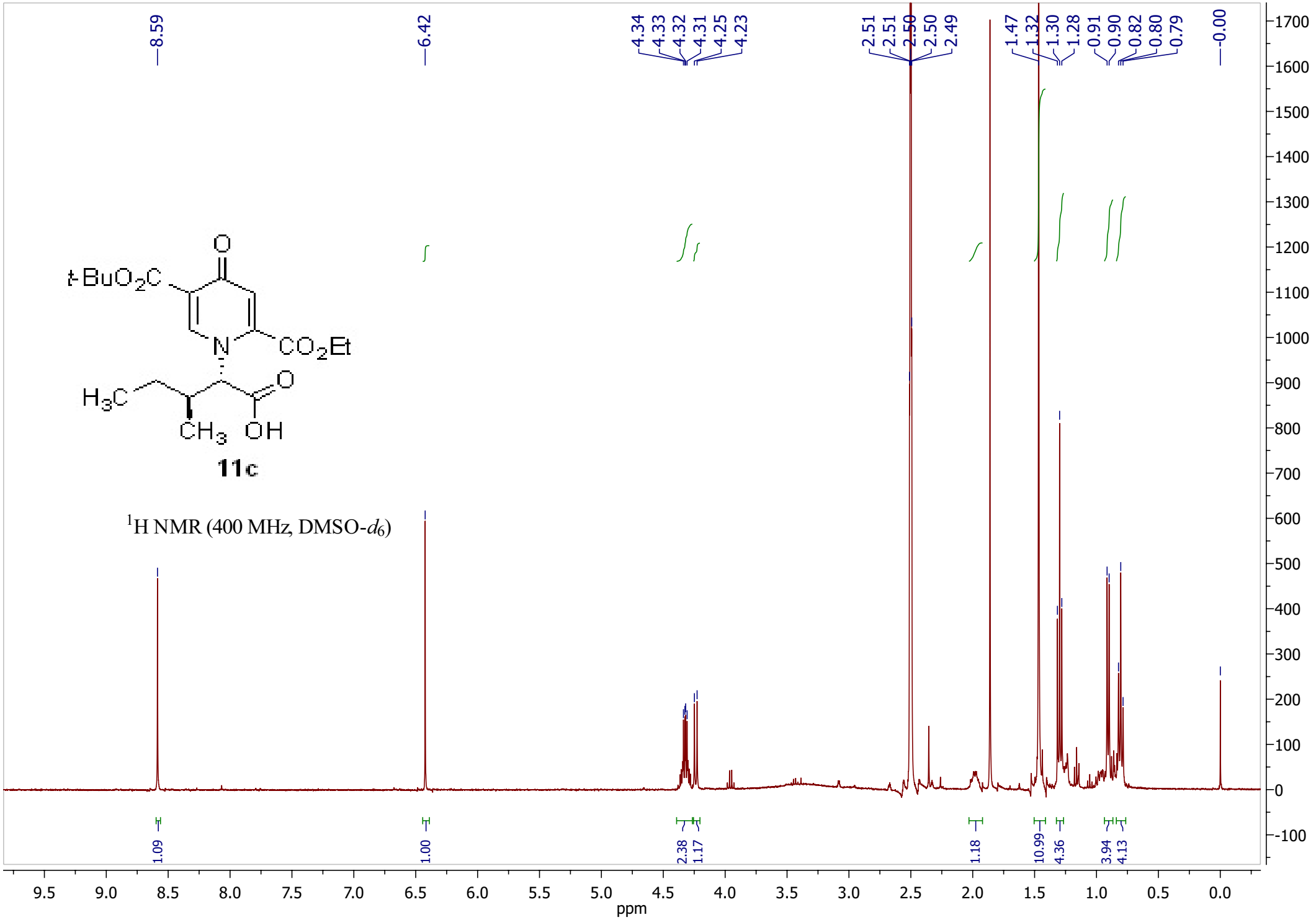

**11b**

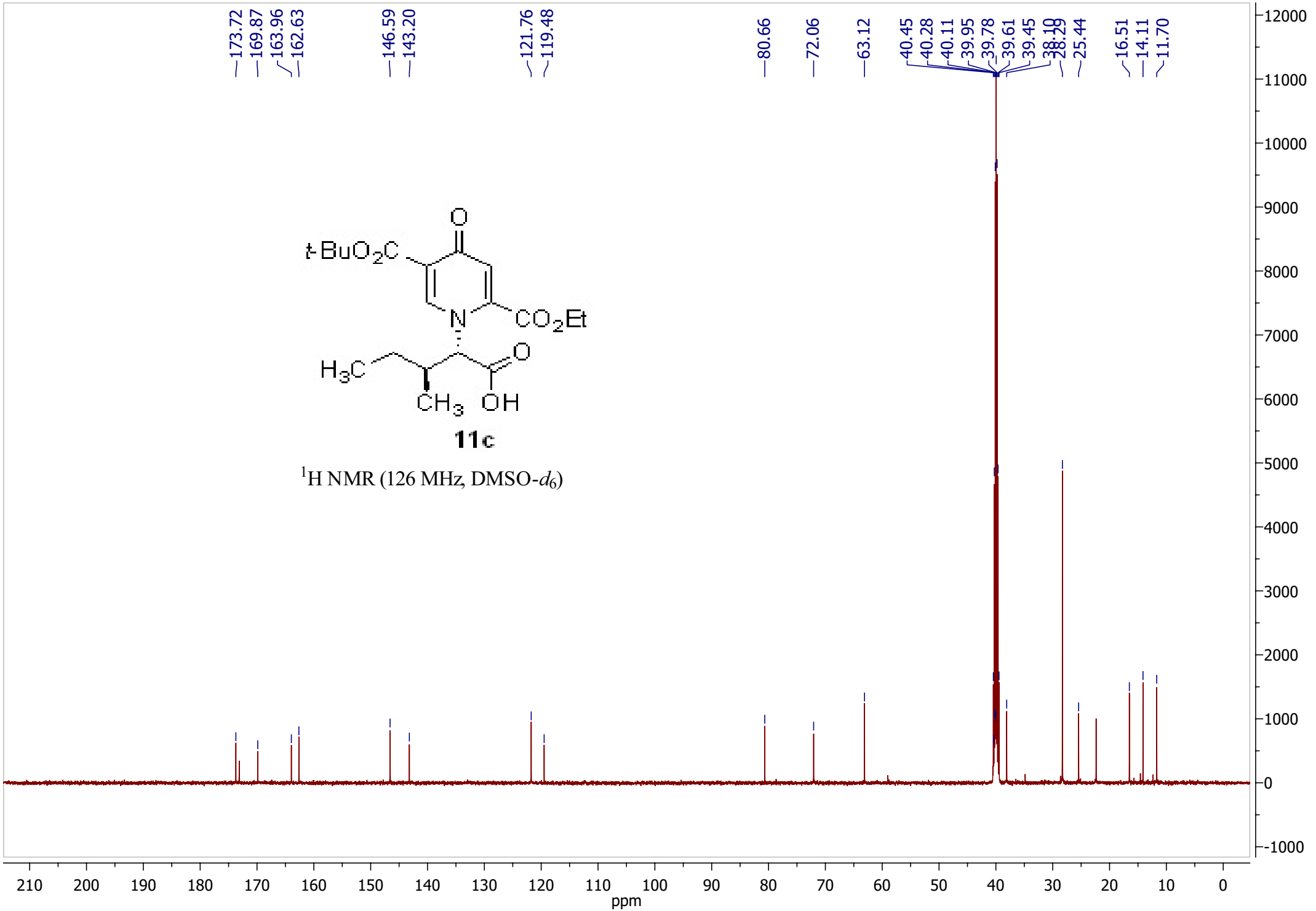
$^{1}$H NMR (400 MHz, DMSO-$d_6$)




**11b**

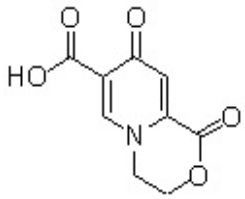
$^{13}$C NMR (126 MHz, DMSO-$d_6$)


8.59
6.42
4.34
4.33
4.32
4.31
4.25
4.23
2.51
2.51
2.50
2.50
2.49
1.47
1.32
1.30
1.28
0.91
0.90
0.82
0.80
0.79
0.00
t-BuO2C
CO2Et
N
O
H3C
CH3
OH
11c
1H NMR (400 MHz, DMSO-d6)
1.09
1.00
2.38
1.17
1.18
10.99
4.36
3.94
4.13
ppm



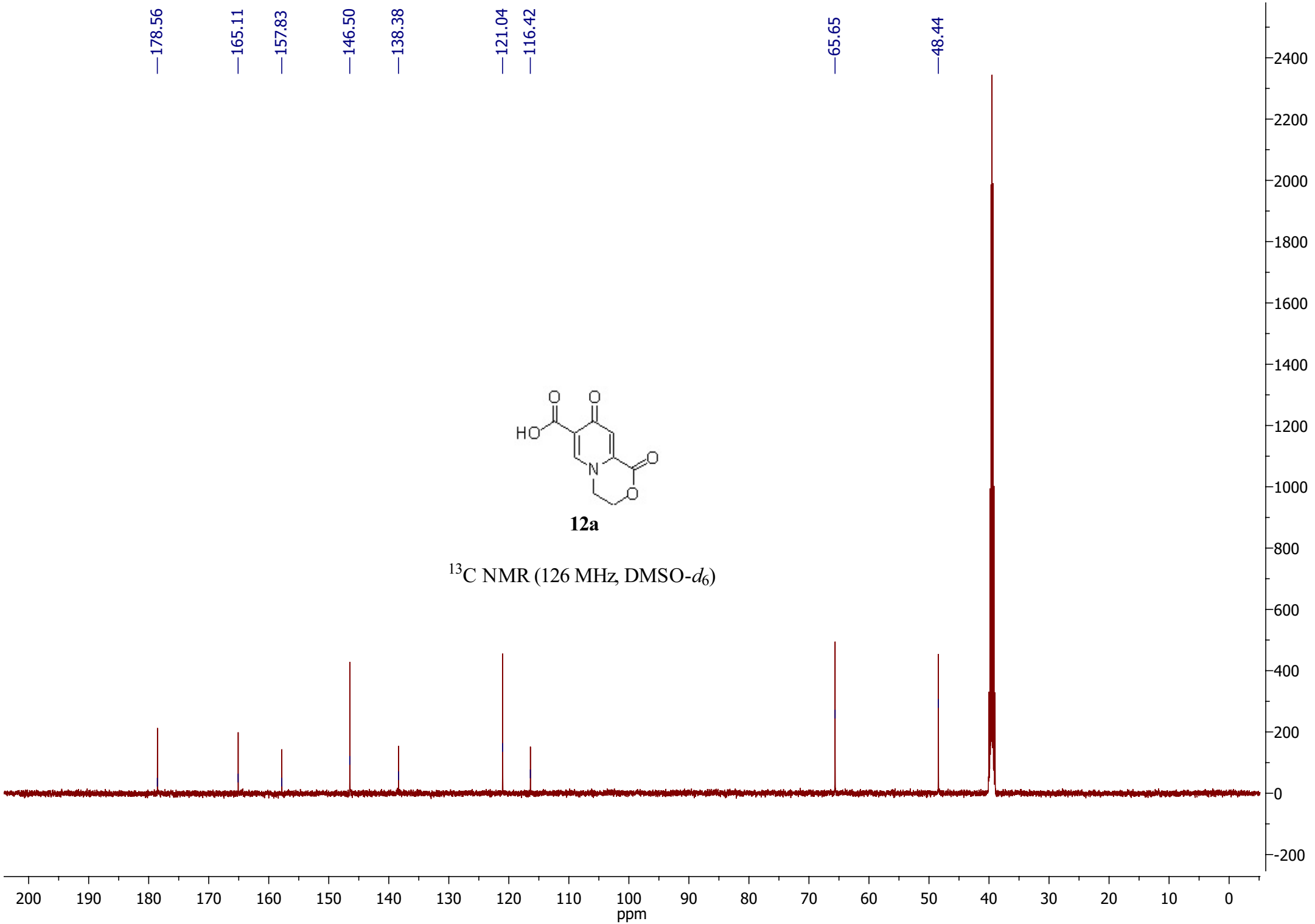

**11c**

$^1$H NMR (126 MHz, DMSO-$d_6$)



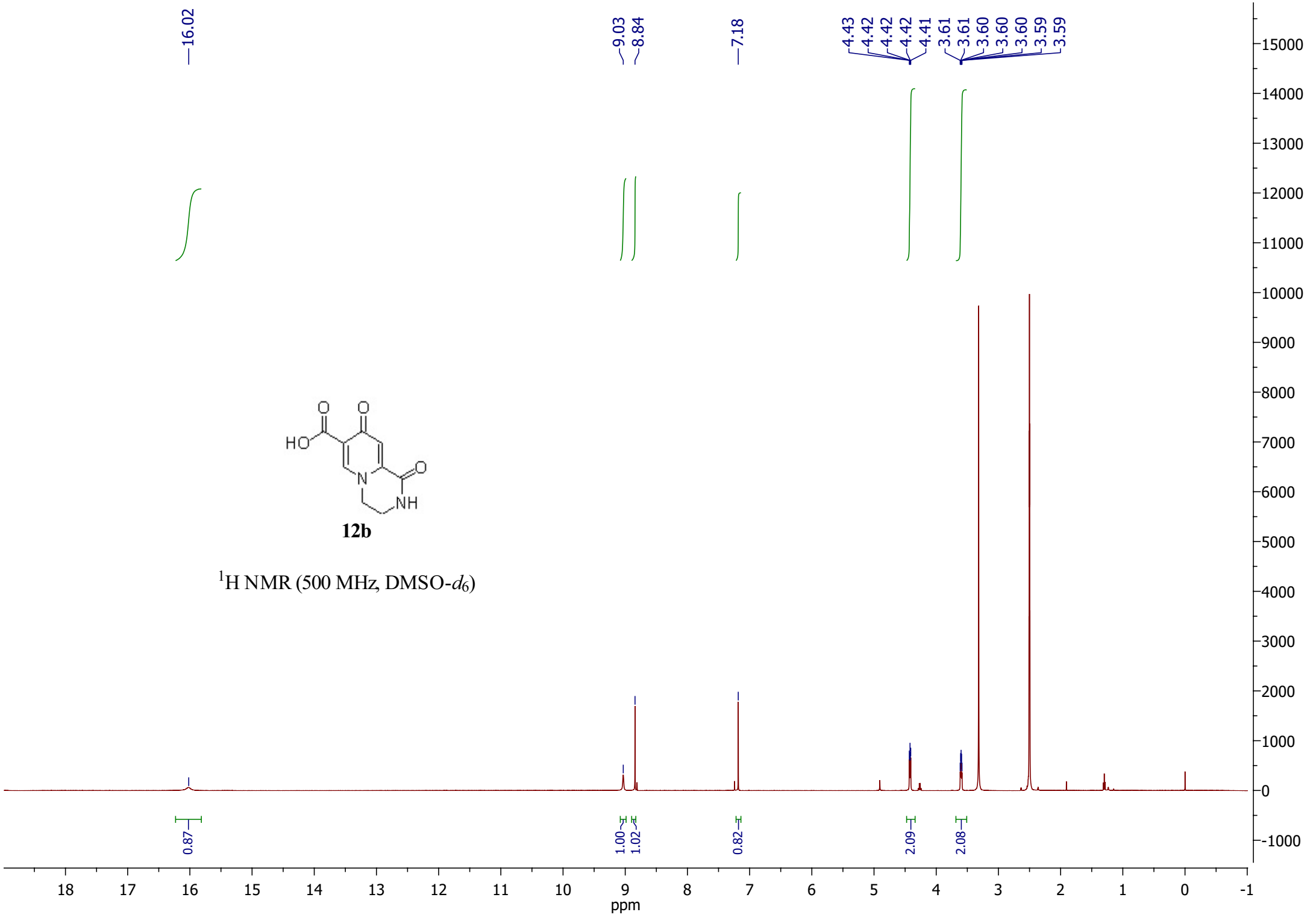
**12a**

$^1$H NMR (500 MHz, DMSO-$d_6$)



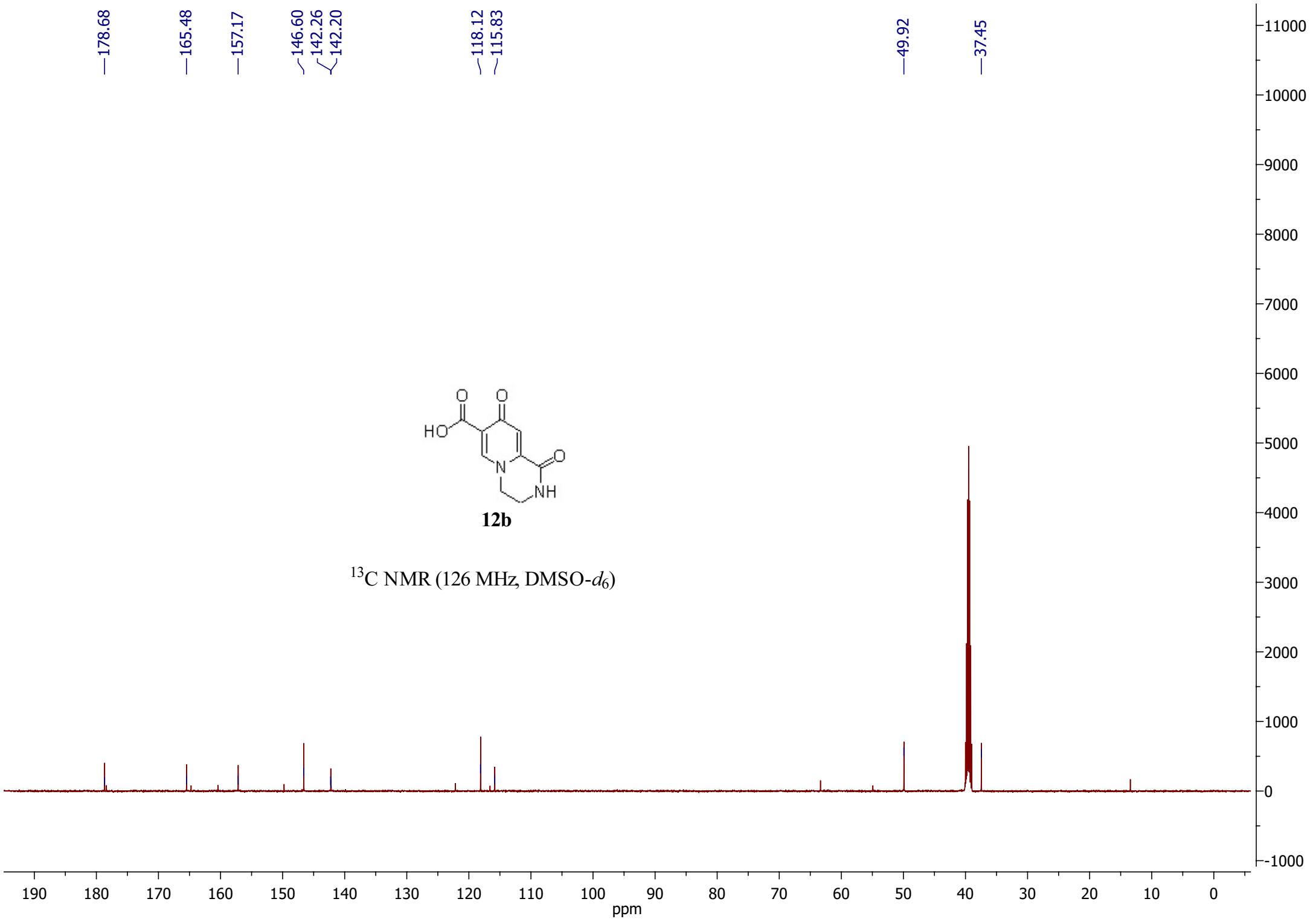

**12a**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**12b**

$^1$H NMR (500 MHz, DMSO-$d_6$)

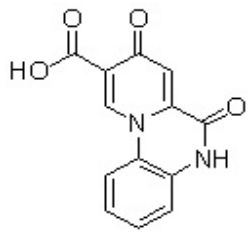






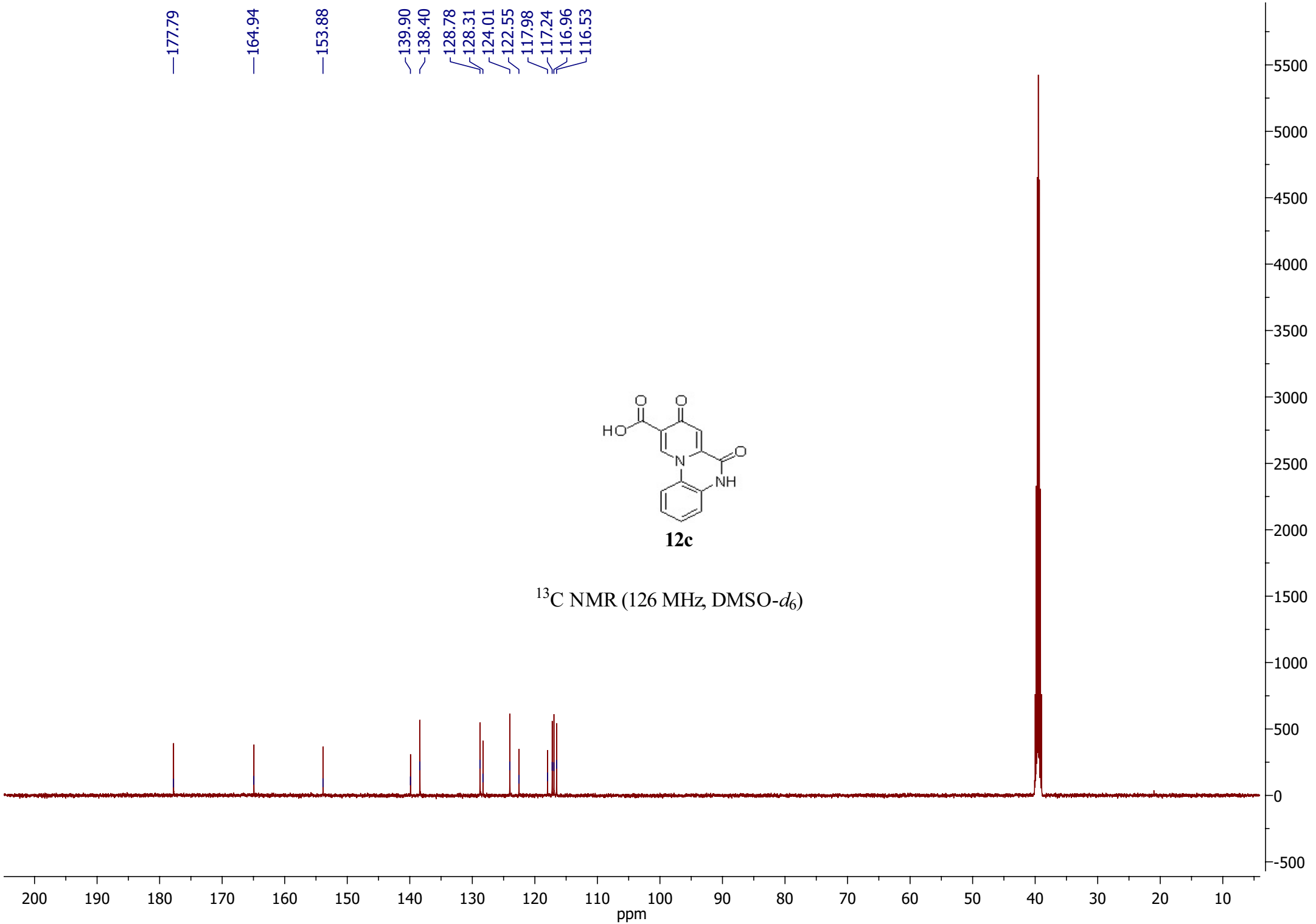
**12b**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



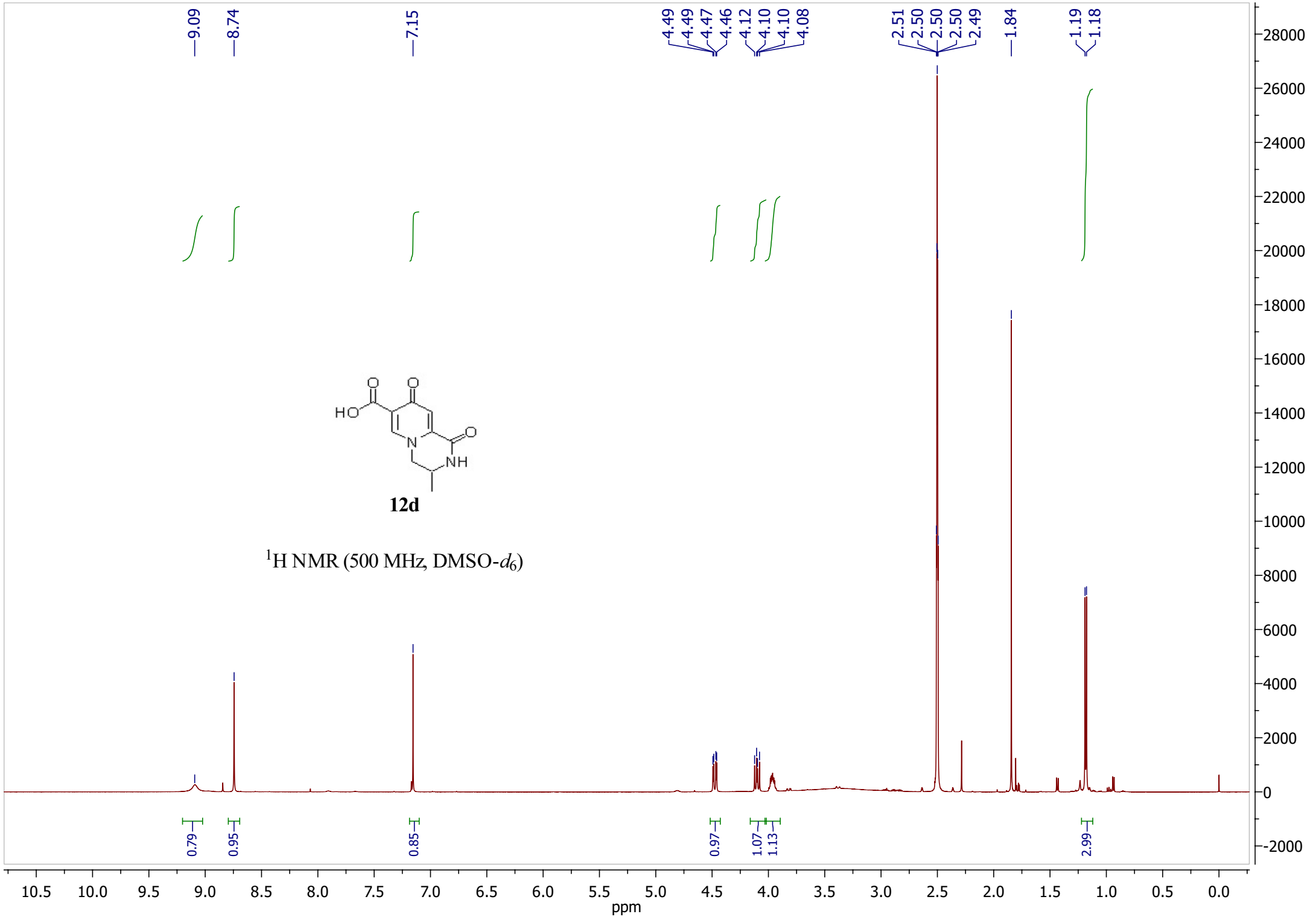
**12c**

$^1$H NMR (500 MHz, DMSO-$d_6$)



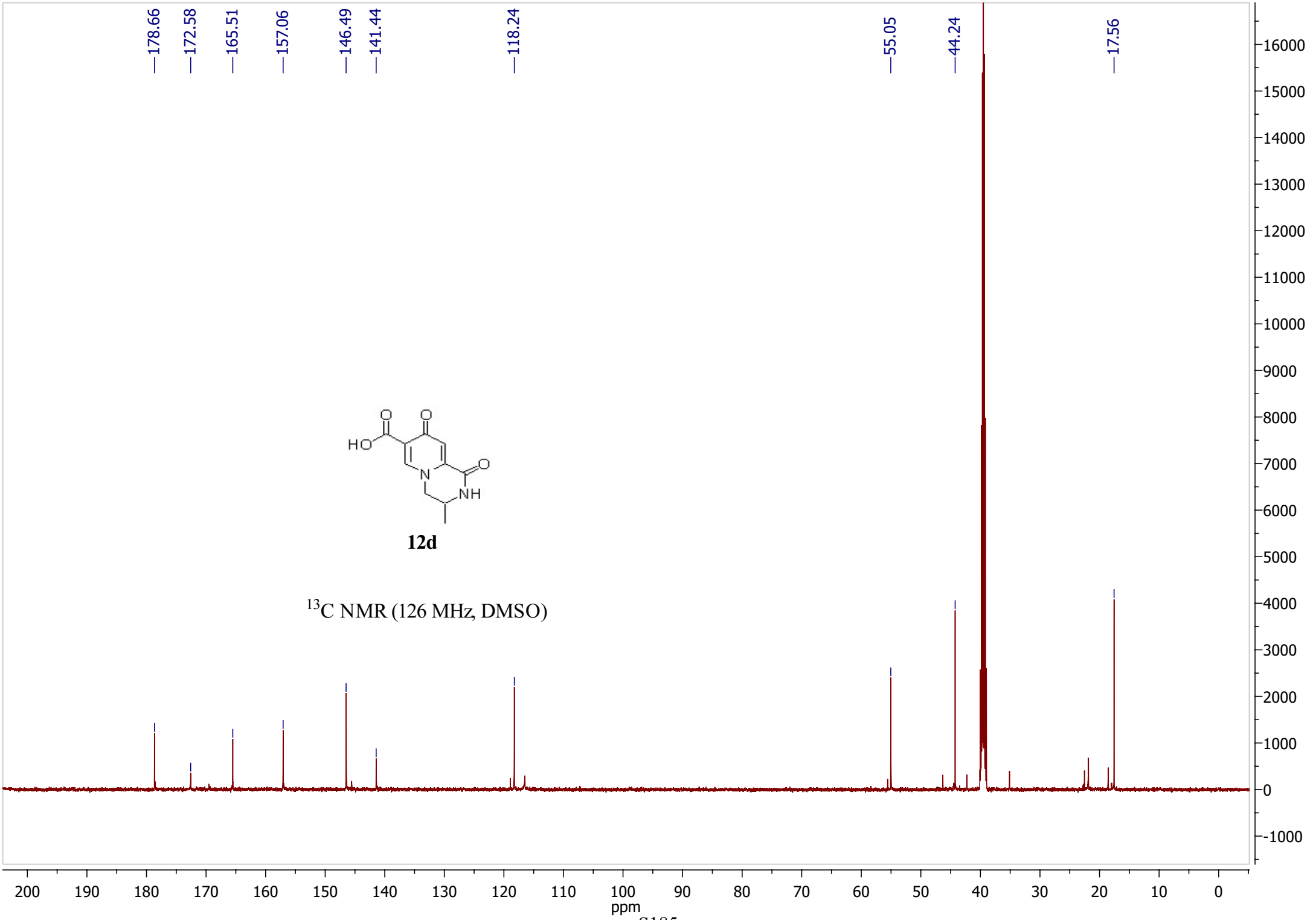

**12c**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



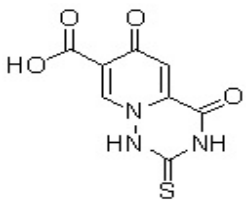

**12d**

$^1$H NMR (500 MHz, DMSO-$d_6$)



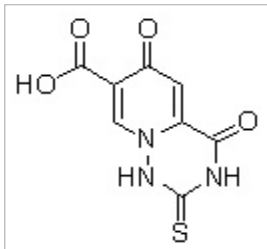

**12d**

$^{13}$C NMR (126 MHz, DMSO)



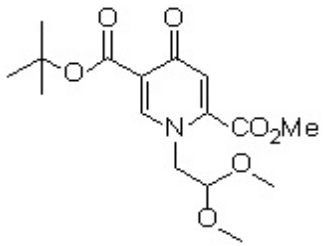
**12e**

$^1$H NMR (500 MHz, DMSO-$d_6$)



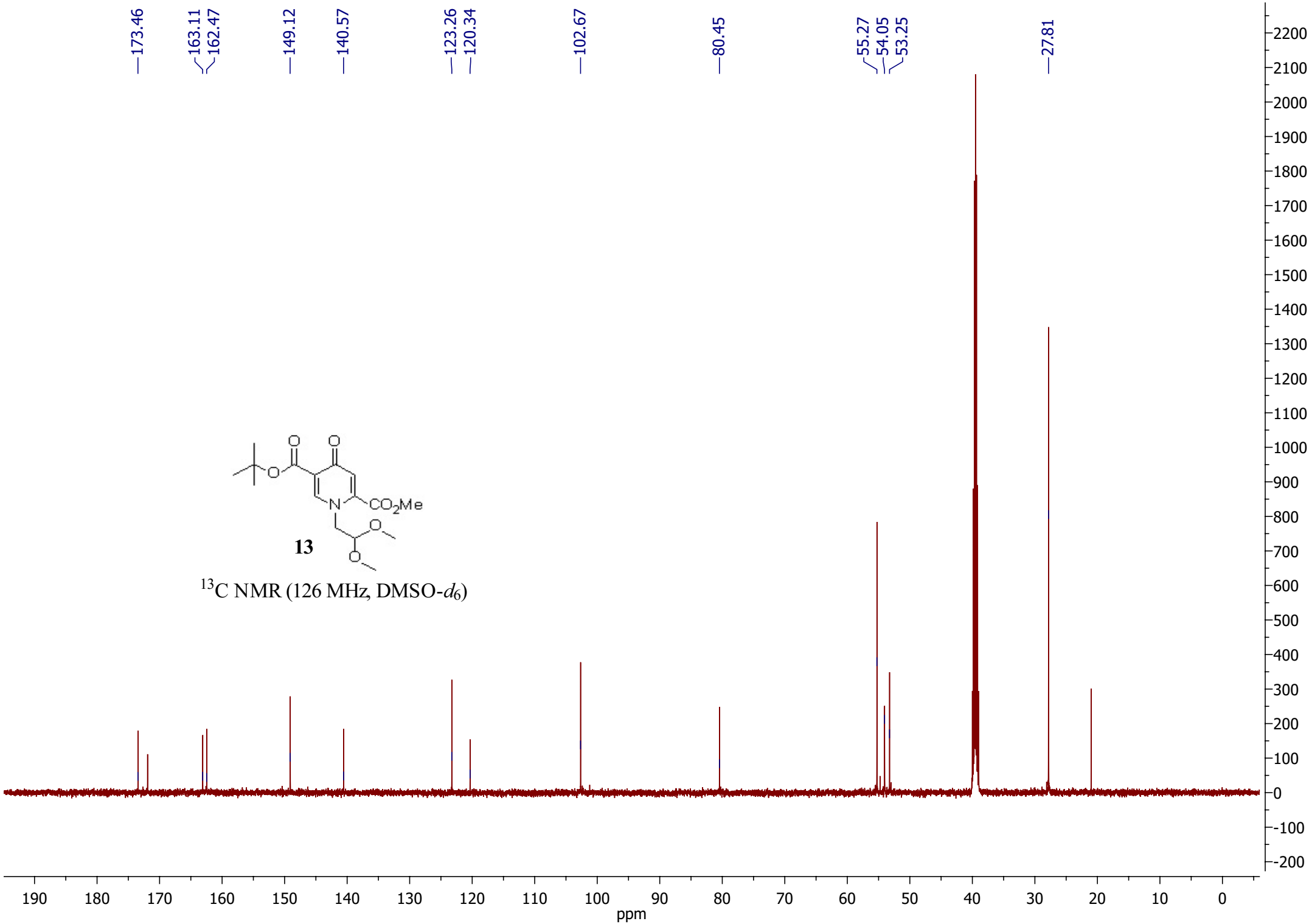
**12e**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)

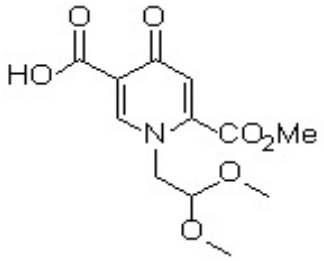



**13**

$^{1}$H NMR (500 MHz, DMSO-$d_6$)

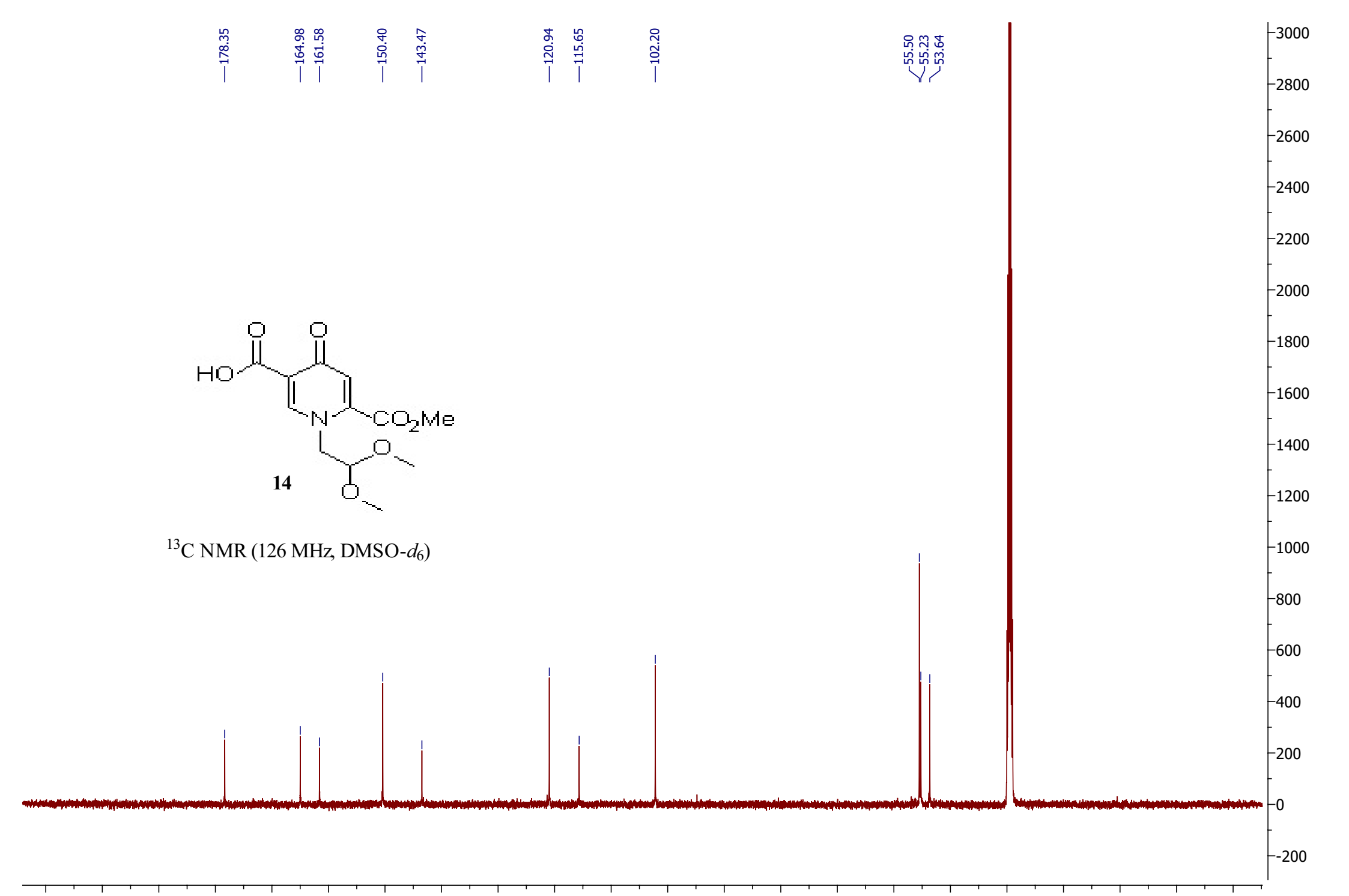



$^{13}$C NMR (126 MHz, DMSO-$d_6$)

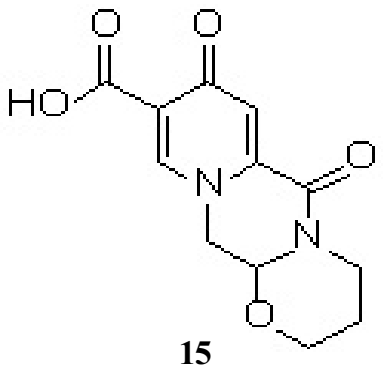


**14**

$^1$H NMR (500 MHz, DMSO-$d_6$)

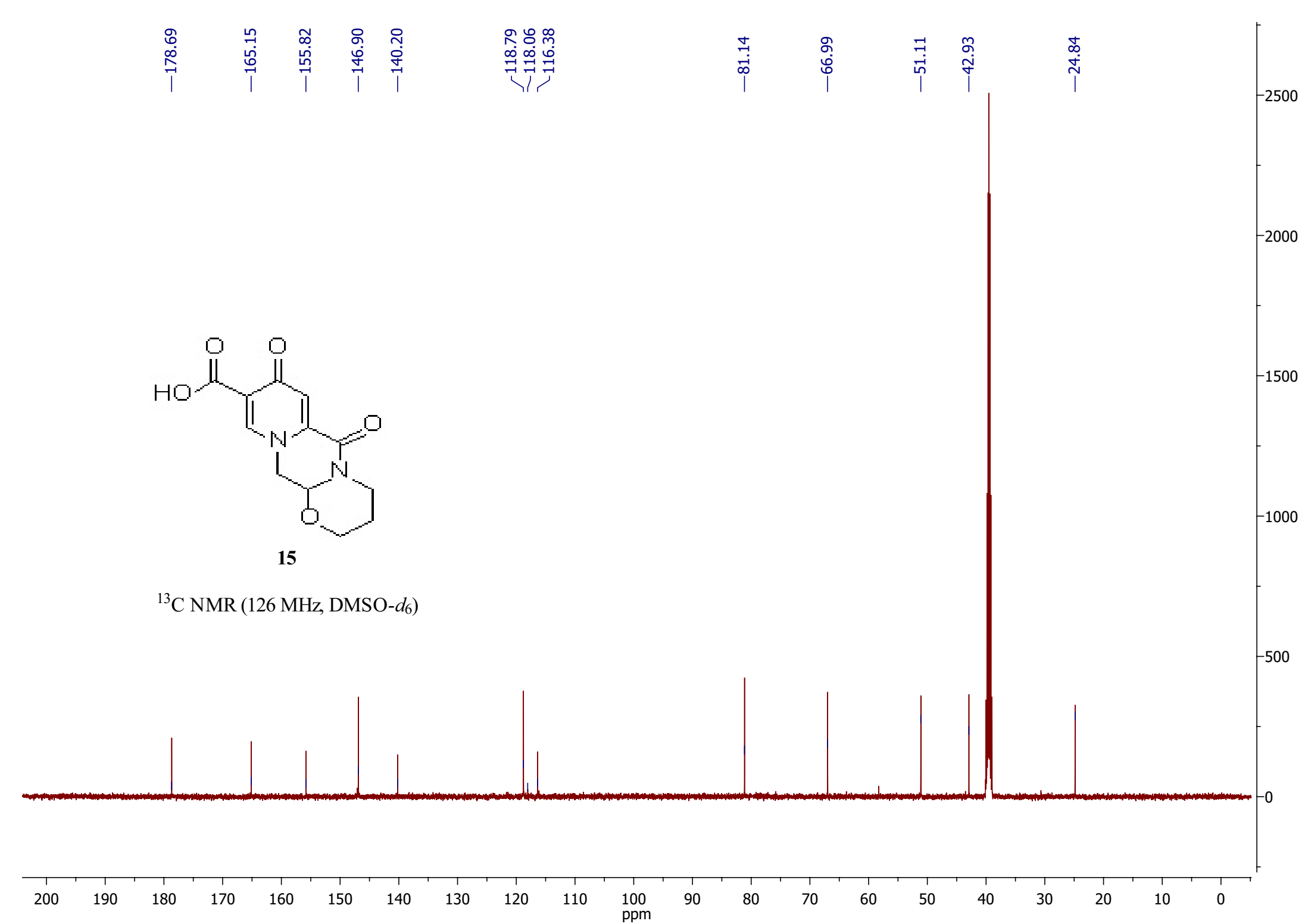



$^{13}$C NMR (126 MHz, DMSO-$d_6$)



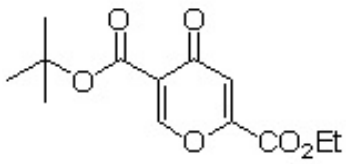
**15**

$^1$H NMR (500 MHz, DMSO-$d_6$)



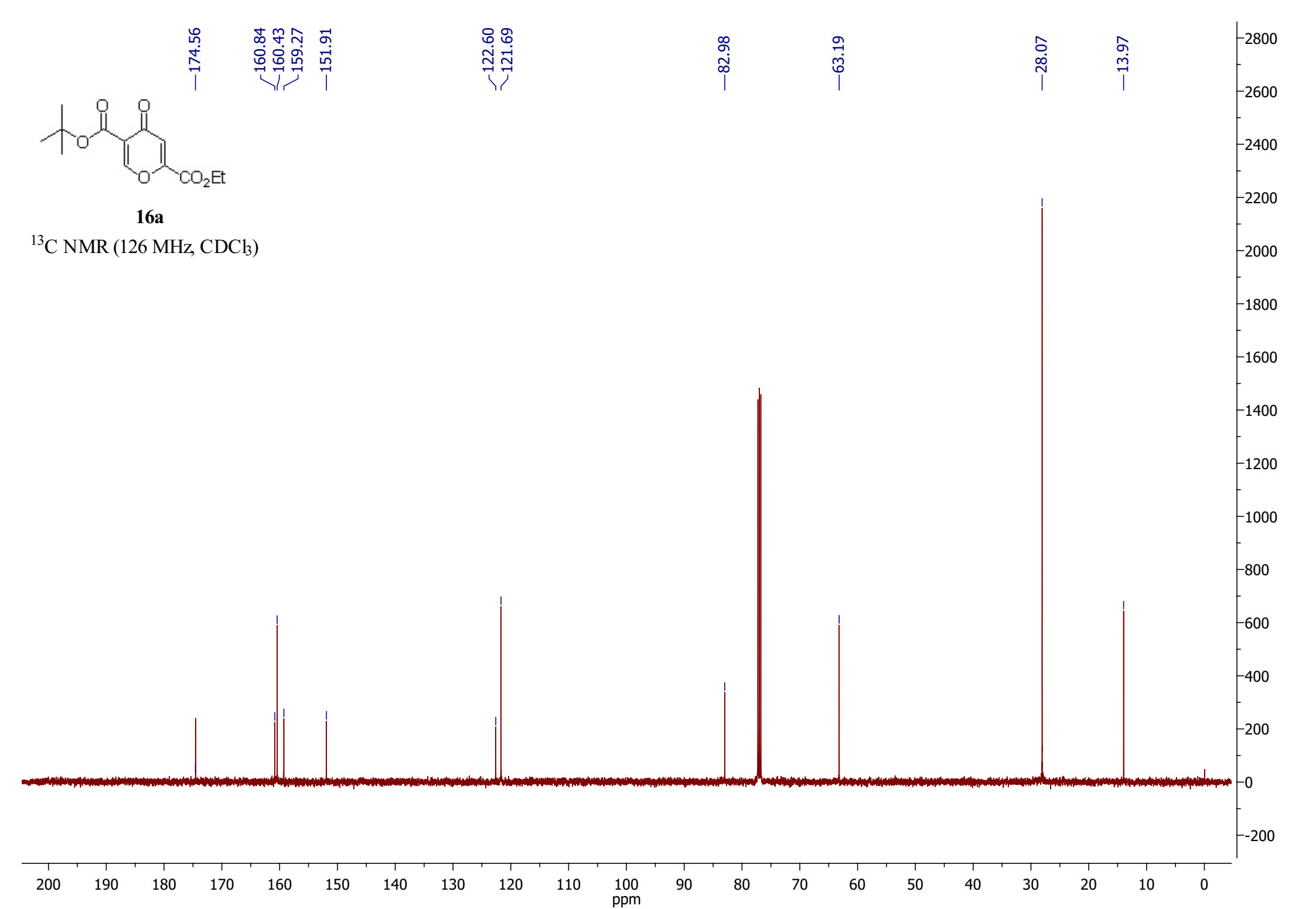

**15**

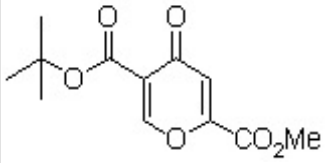
$^{13}$C NMR (126 MHz, DMSO-$d_6$)




**16a**

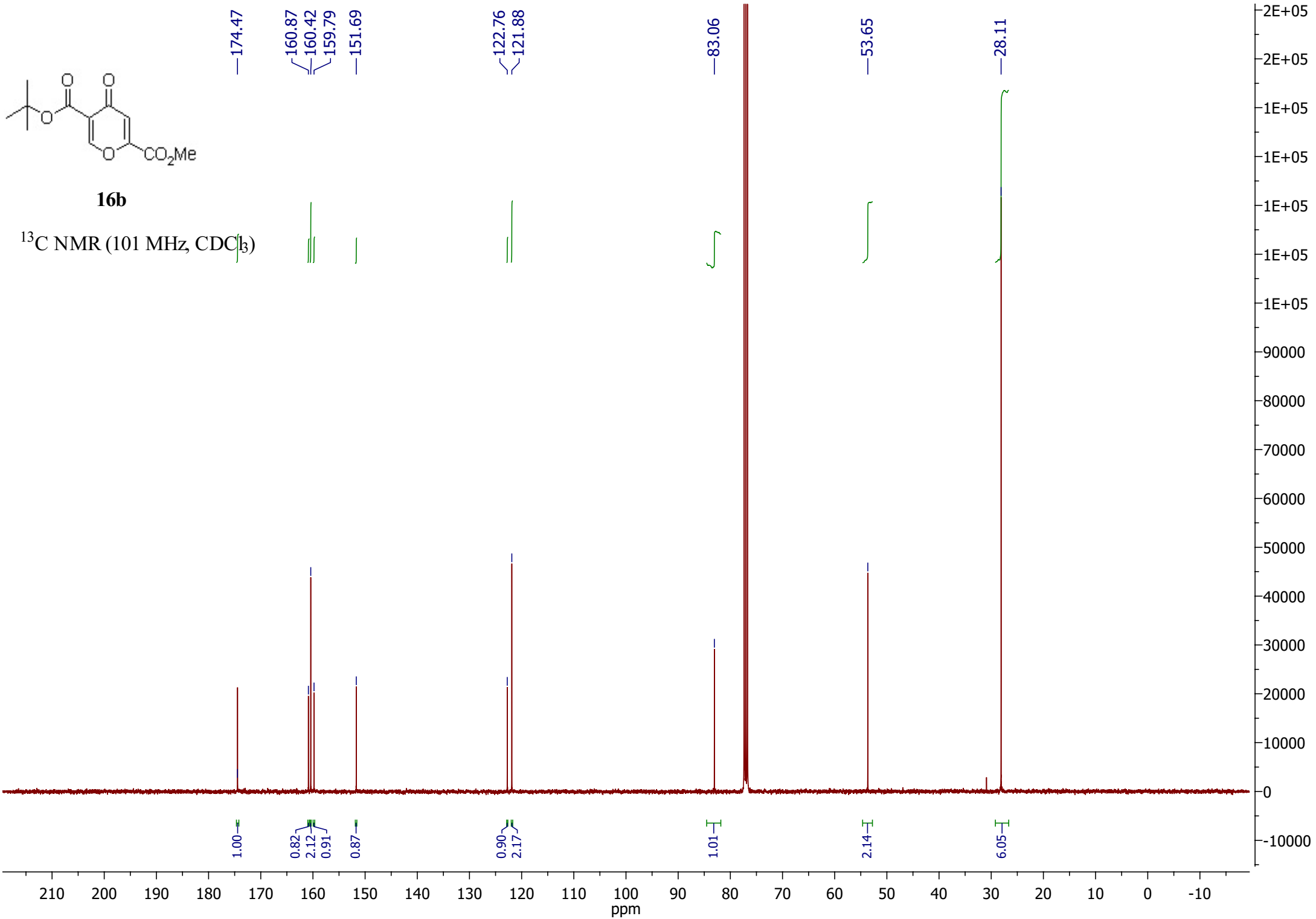
$^1$H NMR (500 MHz, $CDCl_3$)

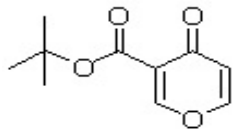

174.56
160.84
160.43
159.27
151.91
122.60
121.69
82.98
63.19
28.07
13.97
CO2Et
16a
13C NMR (126 MHz, CDCl3)
ppm



**16b**

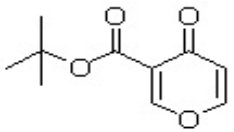
$^1$H NMR (400 MHz, $CDCl_3$)


174.47
160.87
160.42
159.79
151.69
122.76
121.88
83.06
53.65
28.11
CO2Me
16b
13C NMR (101 MHz, CDCl3)
1.00
0.82
2.12
0.91
0.87
0.90
2.17
1.01
2.14
6.05
ppm



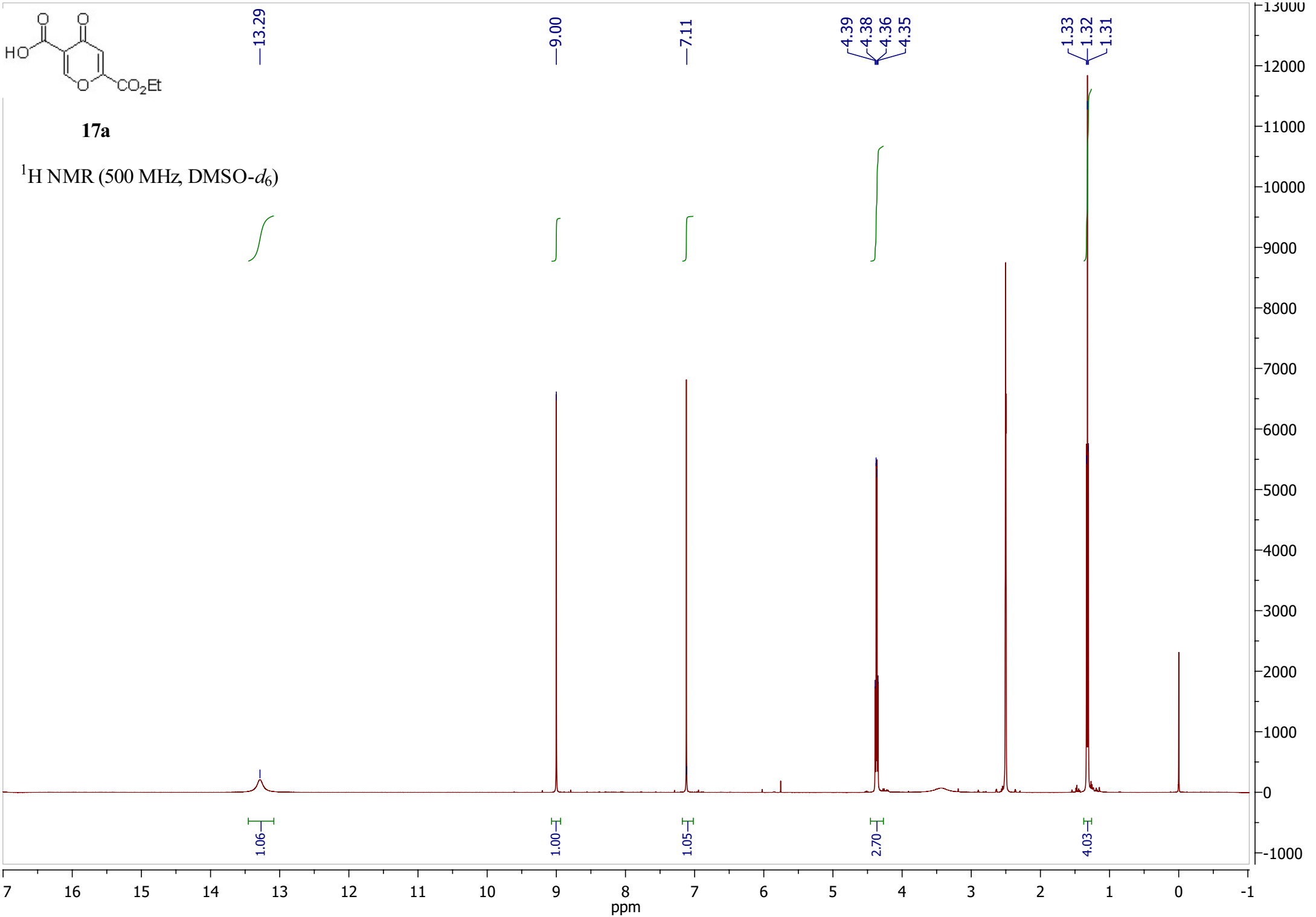
**16c**

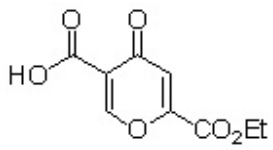
$^1$H NMR (500 MHz, $CDCl_3$)



**16c**

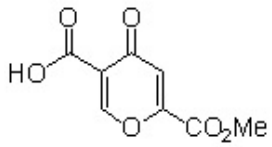
$^{13}C$ NMR (101 MHz, $CDCl_3$)


HO
O
O
O
CO2Et
17a
1H NMR (500 MHz, DMSO-d6)
13.29
9.00
7.11
4.39
4.38
4.36
4.35
1.33
1.32
1.31
1.06
1.00
1.05
2.70
4.03
ppm



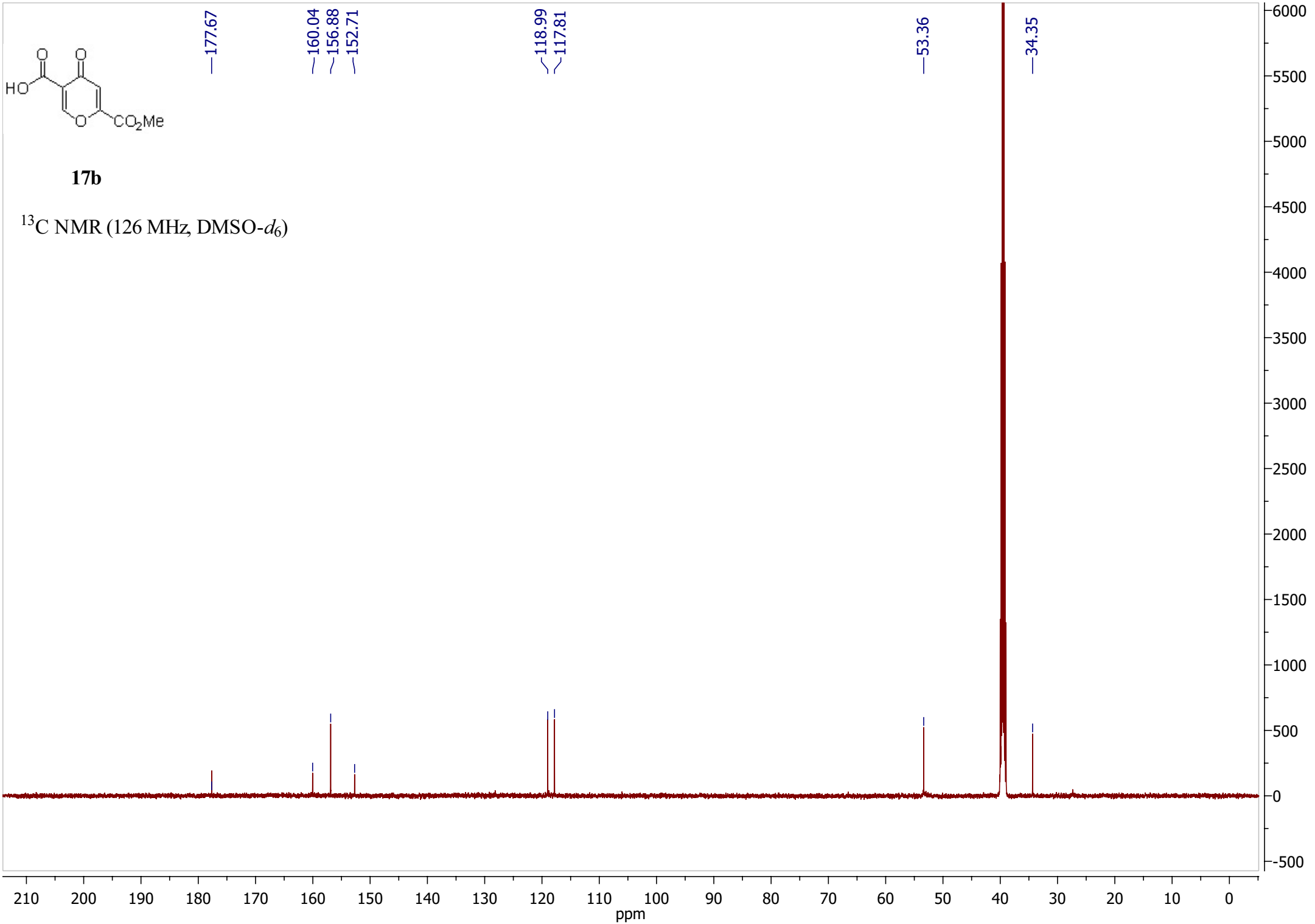

**17a**

$^{13}C$ NMR (101 MHz, $CDCl_3$)



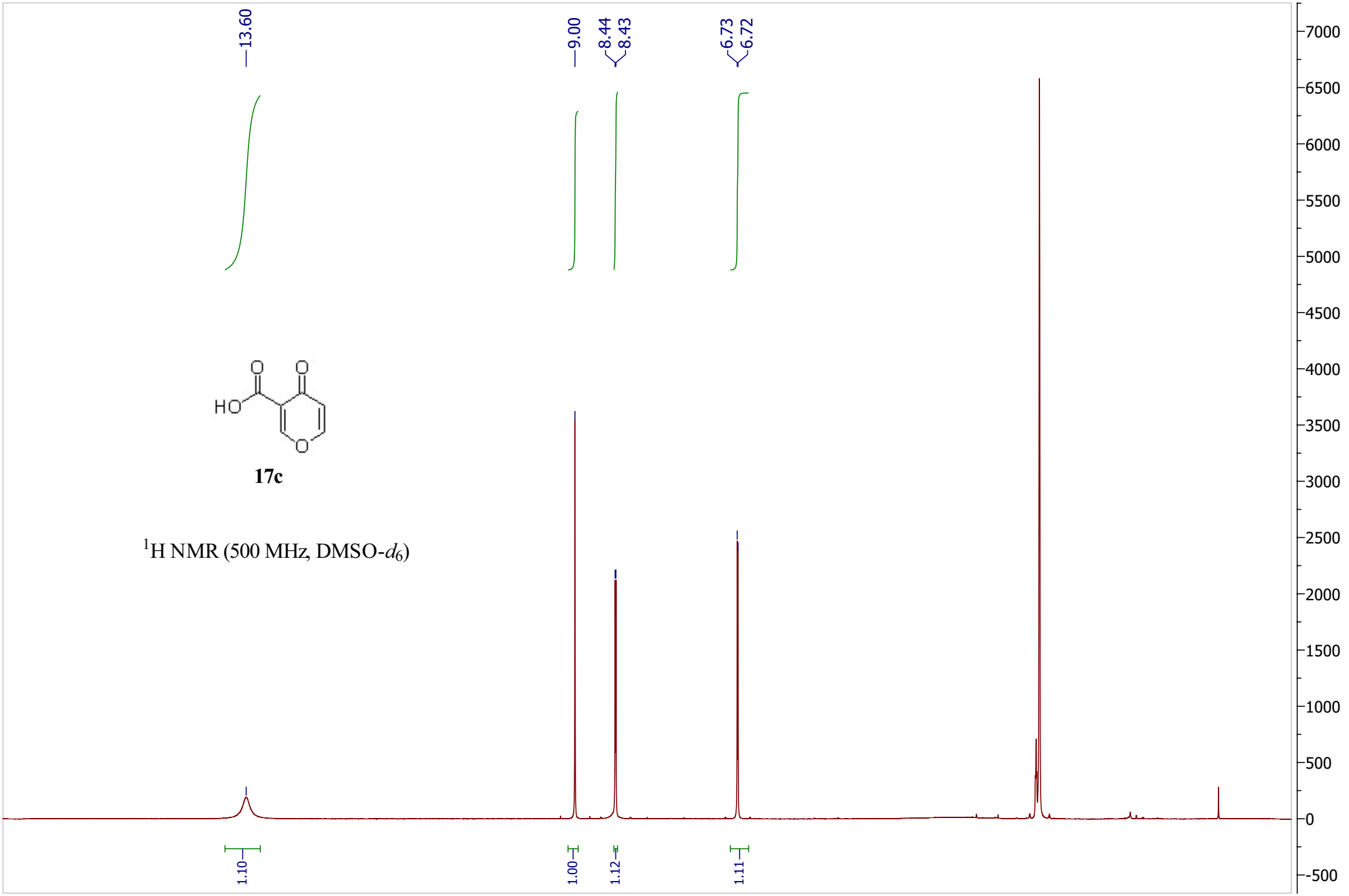

**17b**

$^1$H NMR (400 MHz, DMSO-$d_6$)



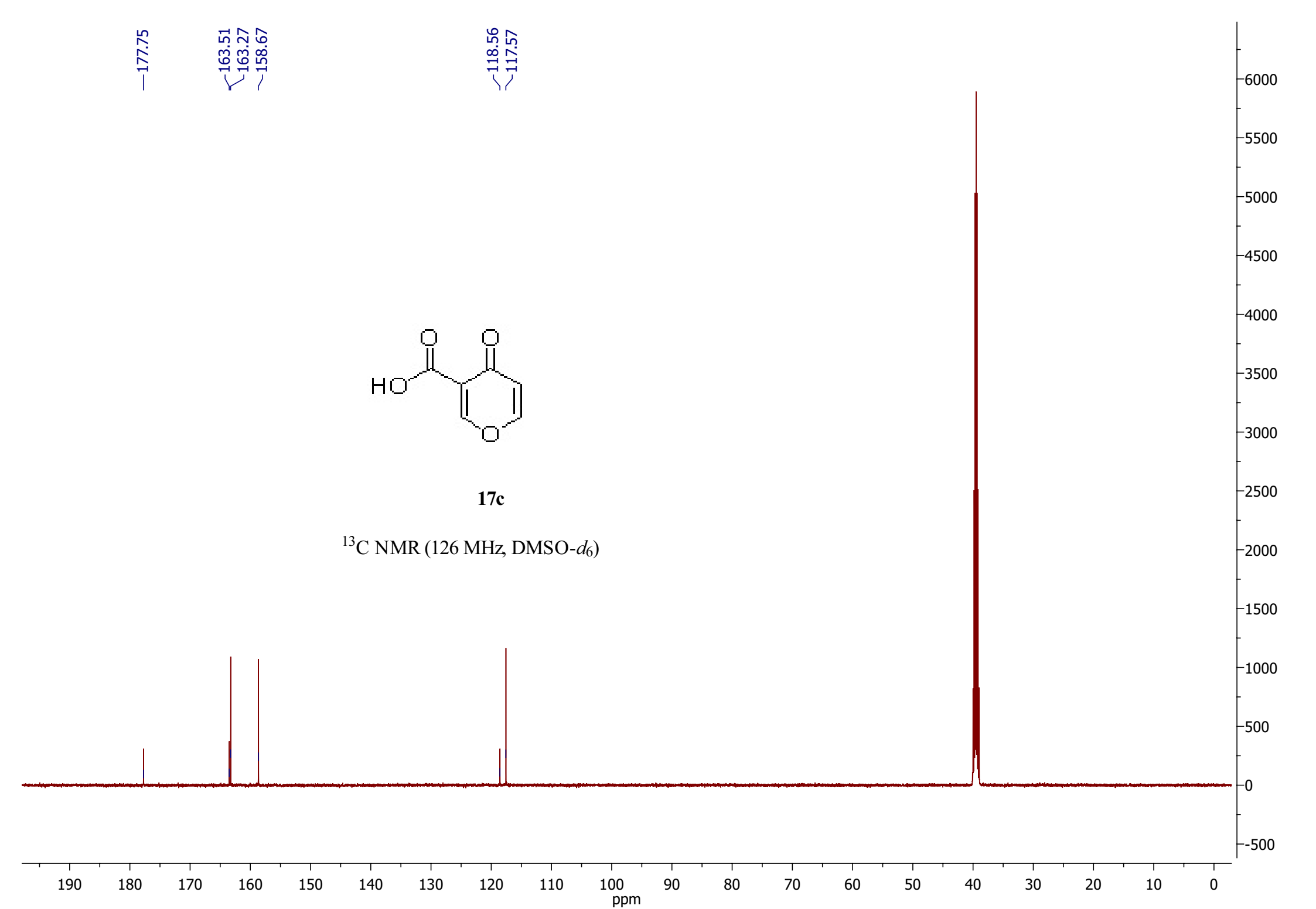

**17b**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)



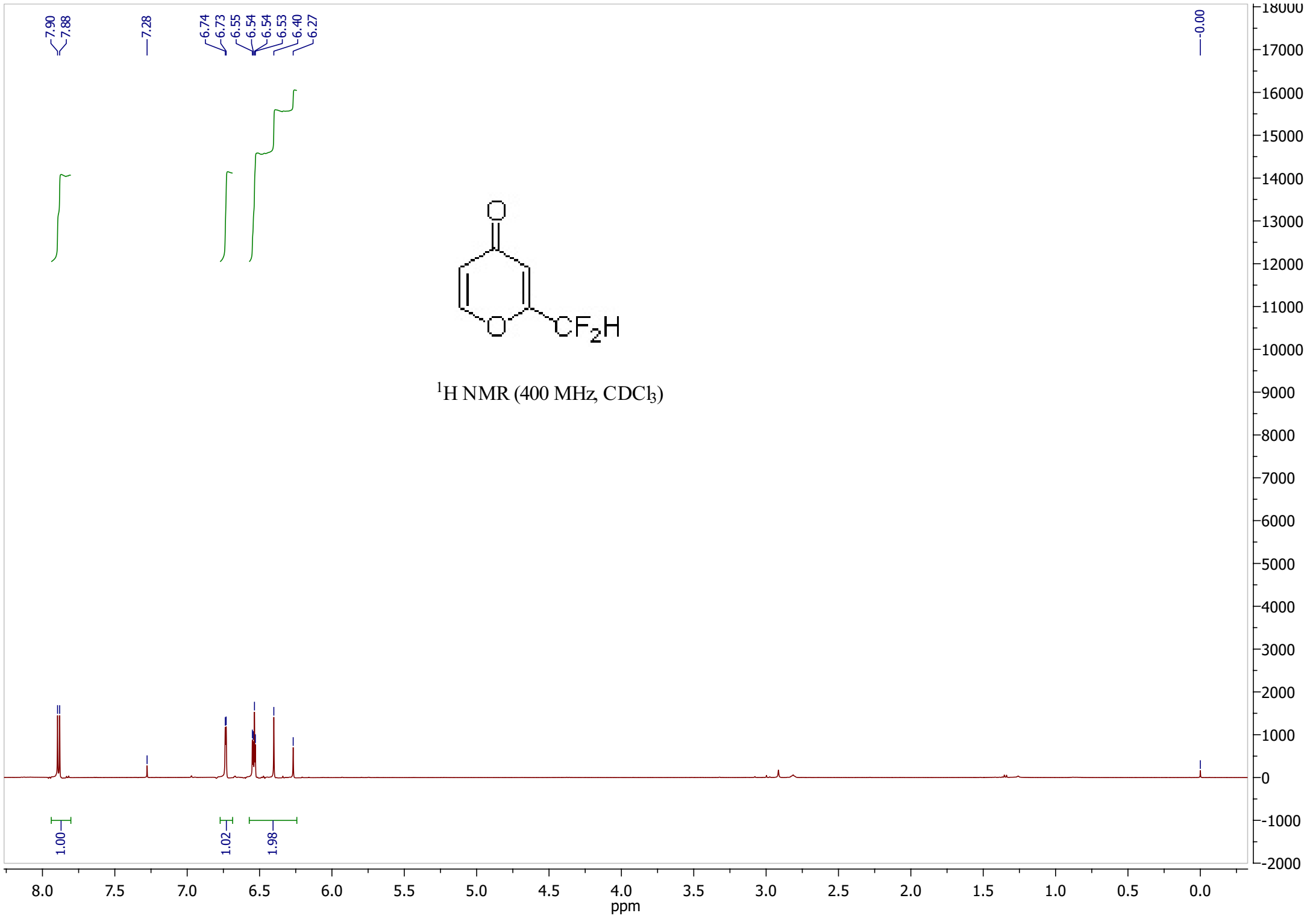

**17c**

$^{1}$H NMR (500 MHz, DMSO-$d_6$)




**17c**

$^{13}$C NMR (126 MHz, DMSO-$d_6$)




$^{1}$H NMR (400 MHz, $CDCl_3$)